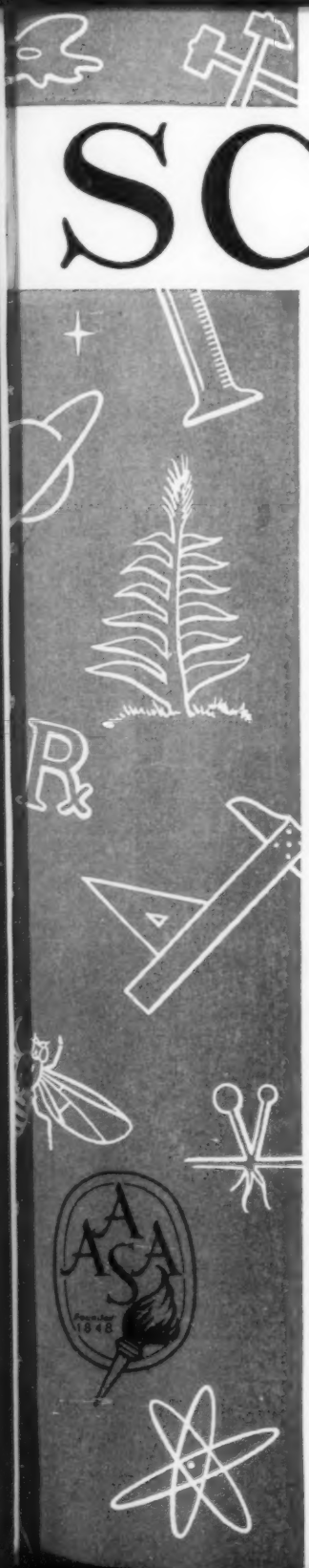

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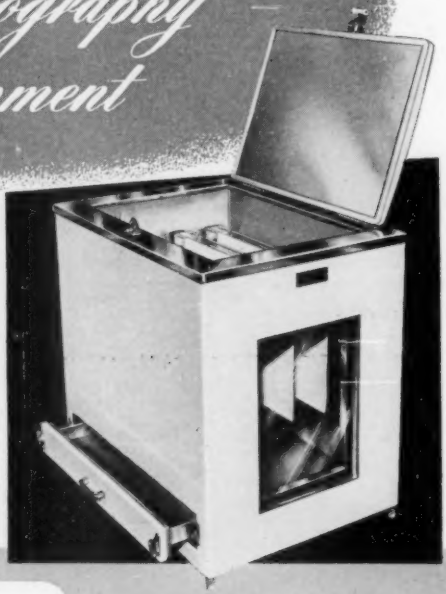

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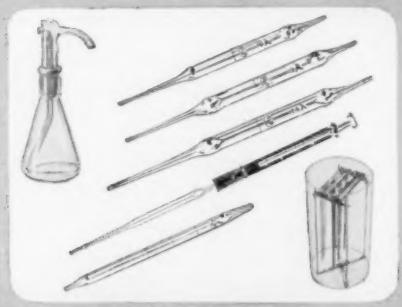

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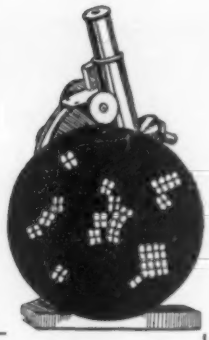

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Conference on Steroid Determination

FROM May 31 to June 4, 1953, there was held at the laboratories of the Worcester Foundation for Experimental Biology in Shrewsbury, Massachusetts, a conference on "Methods of Steroid Determination in Blood and Urine," conducted by the Committee on Arrangements of the Laurentian Hormone Conference, and financed by a grant of $8,900 from the National Science Foundation. Fifty-eight experts from North America and Europe attended as official members of the conference. The nineteen papers delivered and the discussions of them will be published as a volume of *Recent Progress in Hormone Research*, the official publication of the Laurentian Hormone Conference.

The papers covered such subjects as the isolation of hormones from body tissues and fluids, the separation of cortisone and related steroids from blood, and the use of steroids tagged with radioactive atoms as biological tracers.

The members of the conference voted unanimously to authorize Gregory Pincus, chairman of the conference, to transmit to the National Science Foundation their sincere thanks for making possible the meetings, and to express their vigorous endorsement of a policy which makes possible informal, basic scientific meetings of this type, which are desirable not only because of the benefit accruing to the participants, but also because the formal papers and the extensive discussions of the conference are to be made available in the form of a published volume. As a result of such conferences many previously unpublished and frequently controversial and discordant data in an important area of science, in which many investigators are working, are brought forward, discussed, criticized, and evaluated, making possible conclusions regarding the present status of the problems in a particular field, and providing a sounder basis for further investigations. Finally, it was agreed that conferences of this type serve the important function of expediting oral communication among groups of scientists, and thereby not infrequently reveal important details of investigative procedure which have not been adequately discussed or are somewhat ambiguous in published papers.

The British delegates requested that their very sincere thanks should be conveyed to the National Science Foundation for the financial assistance which made possible their attendance at and participation in the conference. They also requested that it should be put on record that in their view the conference has fulfilled a most valuable function in promoting cooperation and good will between workers in the field of endocrinology in the United States and Great Britain.

GREGORY PINCUS
Worcester Foundation for Experimental Biology

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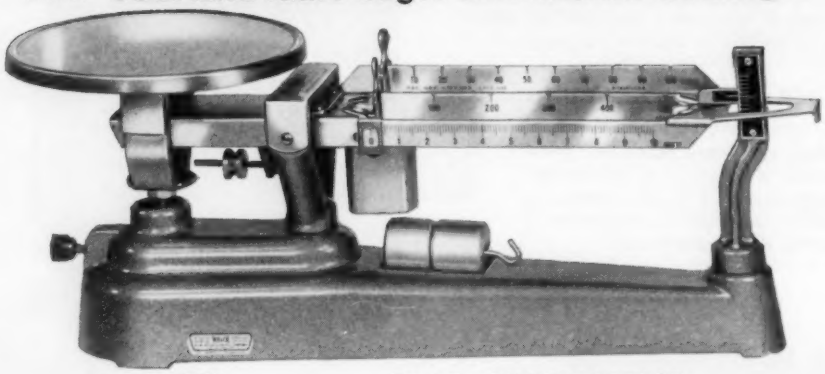

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Free Research versus Design Research[1]

Curt P. Richter

Psychobiological Laboratory, Johns Hopkins Hospital, Baltimore, Maryland

THERE IS A CHOICE before us between free and design research, or as I see it, between supporting the man or the experimental design. Let us support the man.

I bring up a discussion of this choice because I believe it is of vital concern to us as members of one of the committees of the National Research Council, whose chief function it is to pass on research projects. We have much power in our hands. How we use it may affect the entire future of scientific research in America.

We are participants in a great revolutionary movement. For the first time, we as scientists are beginning to hold the responsibility for our future in our own hands. We are asked to pass not only on the scientific merits of the work of our colleagues, but on its anticipated merits for financial support. This movement started both in this country and abroad during World War I and picked up momentum during and after World War II. It has now become firmly established. Before that, scientists received support almost entirely from individual philanthropists, foundations, other organizations, and university funds. Scientists themselves had little to do with the disposition of funds. Now support comes in large part from the various government agencies—a few large public organizations—and funds for research are channeled almost exclusively through committees of scientists.

We, on this and similar committees, hold the purse strings. We distribute or withhold the life-giving funds for research. This gives us much power and responsibility—more than we may realize. We exercise our power in voting on projects; we fulfill our responsibility by trying to vote fairly, intelligently.

This means in the first place that we must try to get as much first-hand information about the man, the project, the setting, as we can; that we do not content ourselves with hearsay; and in the second place, and more importantly, that we try to work out in our minds the philosophy of the future of research—what do we expect from research? and how can we get it? by supporting individual workers, by supporting teams of workers, or by supporting experimental designs? These questions we must answer.

How do we meet this responsibility now? Have we stopped to consider that in most instances all we know about a project is what we see written on a piece of paper—the application blank—words. We do not know the man, we may never have even heard of him. We know nothing about his ability, ideals, or sincerity; about the project we know only what we see in the application. This means that in most instances we must vote the way most of us bet on horses at the races: because we like the name, the number, or the stable.

Under the circumstances we do the best we can. We pick out the one tangible part of the application—the experimental design—how the man plans to work out his project. We are asking more and more questions; aware of this, applicants elaborate their designs in more and more detail. Accordingly this part has come to play a progressively more important role. A vicious cycle has set in. In making an application for a grant before World War II, a few lines or at most a paragraph or two sufficed for the experimental design; now it may extend over 6–8 single-spaced typewritten pages. And even then committee members may come back to ask for more details. How far we have gone in this direction I have seen in this and other committees. We have all seen members with excellent records of research question research plans, often of other recognized scientists, in such detail that, had it been done to themselves in their earlier and more active years, they would most certainly have protested violently. Although done in good faith, this questioning of details by committee members often serves no other purpose than the inflation of our egos, especially when the applicant is a man of some importance.

Under these circumstances, passing the buck has come to be practiced very widely. Projects are passed from committee to committee—to my knowledge in one instance, six committees—largely because at no place along the line did anyone believe that he had adequate information to come to a firm decision. This is a wasteful, time-consuming, discouraging practice.

The researcher has come to play a less and less important part; comparatively little is known about his background, setting, facilities, his sincerity, above all about his imagination, determination, and ability to carry on independent research. He is gradually being reduced to the status of a technician who must follow out in detail a definite plan of research.

We seem to forget: that in the past great discoveries have with few exceptions been made by individual workers, often working in great isolation; that some of the most important discoveries have been made without any plan of research—largely by acci-

[1] Prepared for the Subcommittee on the Nervous System, Committee on Medicine, National Research Council, and read on November 17, 1952.

dent or in dreams, as in the instance of Loewi's Nobel prize-winning discovery; that discoveries have resulted from a general state of what Alan Gregg has called puzzlement—puzzlement at discrepancies in findings—a state of mind which would not lend itself to any accurate verbal description; that there are researchers who do not work on a verbal plane, who cannot put into words what they are doing—whose thinking functions in terms of experiences, subconscious observations—who don't know what they have been after until they actually arrive at their discoveries.

We seem to forget too: that experimental designs only serve a purpose in most instances of confirming what is already known, filling in gaps, adding decimal points; that experimental designs are useful tools devised by statisticians to check on ideas, but that they are not substitutes for ideas; that there may be little relation between a man's ability to devise wonderful experimental designs and his ability to do research; that good researchers use research plans merely as starters and are ready to scrap them at once in the light of actual findings; that experimental designs breed "team research." Research plans are laid out in detail. Men must be found to fit into them. Good research men may be taken away from their own work benches, often never to return. Actual work is often delegated to technicians. Opportunities for getting first-hand information are reduced to a minimum. Opportunities for independent thinking are sacrificed. Often no one person takes responsibility. "Team research" serves a purpose in developing and applying ideas; it rarely produces new ideas. It usually discourages the real researcher and encourages men who on their own would otherwise never have entered research.

In trying to fulfill our responsibilities we must take into account two other factors: the source and amounts of the funds and the fact that we are facing the possibility of full-scale warfare. Our funds come from the public treasury through one or more channels; they are greater than ever before, greater than any of us would have dreamed of before World War II. The cry is still for more and more funds. Do we want quality or quantity in our research?

Large funds encourage great enterprises—great experimental designs. They encourage great "teams of workers." They take good research men away from their work benches to direct many technicians. The use of such large sums from the public treasury for research must be justified—public-spirited men are likely to want to know how the funds have been used. This means that we, members of this and similar committees, as men who are responsible for the distribution of funds from the public treasury, are naturally prompted to play safe, not to gamble with public funds. Sensitive to these responsibilities we feel ourselves urged to ask for details of designs, expenditures—we hesitate to give the researcher a free hand. We have to ask ourselves whether this is a wise, farsighted policy.

Most importantly in many instances we must face the problem of how a project fits into the war needs. When the needs are immediate, it is the project, the design, that counts. Who does the work is often relatively unimportant. It becomes a technical job. Great pressures are being brought from many angles to produce results for immediate use. Shall we sell the day to serve the hour?

What can we do? First of all let us get all the facts we can about the worker, visit him ourselves whenever possible and see him at work. Try to convince ourselves of his ability and sincerity. Find out how his project fits into his scheme of things. See the setting and the facilities offered by his university or community.

Let us try to adjust the funds to his needs.

Let us try to help improve the conditions of research for the individual worker. This means longer grants—fewer reports—less paper work.

Let us not ask men for detailed reports until they have completed their jobs. Half-finished reports only clutter up other men's minds and create confusion in the literature.

Let us try to give the funds for research with as few strings attached as possible, without asking a man exactly what he is going to do and why.

Let us not mistake experimental design for ideas.

Let us encourage researchers to return to their work benches; to make first-hand observations; and let us question whether a proposed "team research" is a product of experimental design or whether it grows out of genuine supplementation of contributions.

Let us remember what Arthus (*1*) said, "Indeed it is not in the turmoil of social life, not through academic chats nor laboratory gossip that we come to see the light, that interpretations become clear, that experiments are conceived, and conclusions reached. It is through solitary, profound, and sustained meditation. In order to make some progress in the experimental sciences one must meditate a great deal." He should have added that ideas do not often come from big conferences and meetings. Let us not take men away from their work for many useless conferences. Let us give them time to think consecutively.

Let us be careful how we handle a researcher's ideas. They belong to him. When he puts them on application forms, let us not broadcast them, scatter them far and wide to scrupulous and unscrupulous hands. Public agencies do this now with the result that authorship of ideas is often forgotten or ignored. The researcher's satisfaction comes from finishing a job—his own. He is human. It may have taken him years to work out his ideas. In wartime, yes, all ideas must be pooled and as quickly as possible. But not in peacetime.

Let us try to educate public agencies and legislators to see the importance of backing individuals—of betting on them—giving them greater freedom. Government agencies can do this. They have done it in Great Britain.

Let us discourage the great practice of passing the buck, avoiding responsibility by passing projects from committee to committee, rather than by getting first-hand information.

The choice before us, experimental design or free research, the project or the man, has many ramifications, but it concerns the mainspring of the entire operation, the future of research in America. Let us support the man.

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Inactivation of Vaccinia Virus by a Diffusible Component from Hydrolyzed Hyaluronic Acid

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PREVIOUS STUDIES from this laboratory have shown that various preparations of hyaluronic acid inactivated vaccinia virus grown in cell culture, and that this effect was markedly increased when the acid was hydrolyzed by hyaluronidase added to the culture medium (*1*). Experiments have, therefore, been carried out to identify the virus-inactivating component or components. In this preliminary note we describe experiments showing that: (a) the virus-inactivating substance is freely diffusible through a cellophane membrane; and (b) the substance, or one of its components, is in all probability glucuronic acid or a glucuronide.

The procedure in 10 basically similar experiments was as follows: an 0.5% solution of purified umbilical cord hyaluronic acid was prepared in 0.1 *M* acetate buffer pH 6.0 containing 0.1 *M* NaCl and dialyzed overnight at 4° against approximately 10 volumes of the same buffer. A purified preparation of dialyzed testicular hyaluronidase (activity 1000 TRU/mg;[4] final concentration 1 : 1000) was then added to the hyaluronic acid and the mixture incubated for 48 hr at 37° in the presence of toluene. A sample of the hydrolyzate was removed and stored at – 20° C, and the remainder dialyzed in cellophane tubing against distilled water at 4° until, as judged by colorimetric tests (*2, 3*), no further N-acetyl glucosamine or glucuronic acid diffused through the membrane. The diffusate (material passing through cellophane) was concentrated to the original volume by lyophilization. The four materials (i.e., hyaluronic acid, hydrolyzate, dialyzate, and diffusate) were sterilized by heat (10 min at 75° C) or filtration and tested together for viral inactivation against dermo or Levaditi vaccinia virus. Tests were carried out on: (*a*) rabbit skin; (*b*) cell cultures; (*c*) the chlorioallantoic membrane of chick embryos; and (*d*) the hemagglutination reaction. Reducing substances, glucosamine, and glucuronic acid were estimated in each fraction. Approximately 50% of the original N-acetyl glucosamine and glucuronic acid present in the hydrolyzate was recovered in diffusible form.

The most striking results were obtained in rabbit skin, and a summary of a typical experiment is given in Table 1. In this experiment equal volumes of diluted virus and test material were incubated at pH 6.0 for 4 hr at 37°; the same virus suspension was incubated with buffer alone as a control. Groups of 4 rabbits then received 0.5 ml of each mixture intradermally, the development of lesions being recorded after 3, 5, and 7 days. Typical lesions developed after 3 days from control injections and in those where virus had been treated with either hyaluronic acid, hydrolyzate, or dialyzate; in the two latter cases the lesions were fre-

TABLE 1

INACTIVATION OF VACCINIA VIRUS BY DIFFUSATE FROM HYDROLYZED HYALURONIC ACID: INTRADERMAL INOCULATION IN RABBITS

(All materials dissolved in 0.1 *M* acetate buffer, pH 6.0)

Test material	Virus dilution*	Type of lesion†
Hyaluronic acid‡	10^{-2}	+++
Hydrolyzate	10^{-2}	+++++
Dialyzate	10^{-2}	+++++
Diffusate	10^{-2}	—
Buffer control	10^{-2}	++++

* Dermo virus, egg-passage strain.

† ++++ Edematous, necrotic lesion, approximately 3–5 cm in diameter; +++ similar lesion without visible necrosis; — no visible or palpable lesion.

‡ Wyeth Institute of Applied Biochemistry, batch 215–2.

[1] James Hudson Brown Memorial Fellow.

[2] Supported by a Research Grant from the National Institutes of Health, USPHS.

[3] With the technical assistance of Robert A. Roosa and Arthur G. Tyrol, Jr.

[4] Kindly supplied by J. Seifter from the Wyeth Institute of Applied Biochemistry.

quently as large as or larger than the control lesions. However, injections of virus treated with diffusate produced at most a small pink spot on the third day, which, in the great majority of cases, faded completely by the 5th to 7th day. Thus, in a series of 9 experiments with diffusates from various samples of hyaluronic acid, highly significant suppression was obtained in 8 instances and at least a 50% reduction in the ninth test. In other experiments, serial dilutions of diffusate-treated virus were inoculated intradermally in rabbits. Compared with virus incubated in buffer at the same pH, the titer of treated virus was reduced by at least 1 log. Hyaluronic acid alone caused some suppression in an occasional animal.

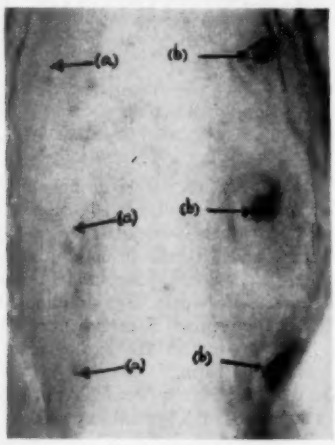

FIG. 1. Effect of incubation with synthetic glucuronic acid on vaccinia virus infection in rabbit skin. Levaditi strain (egg passage) diluted 10^{-3} incubated 4 hr at 37° with an equal volume of: (*a*) 5% glucuronic acid in acetate buffer pH 5.9, and (*b*) 0.5 *M* acetate buffer pH 5.9. Arrows mark injection sites. Note large, necrotic lesions from untreated virus and complete suppression with glucuronic acid-treated virus. Photographed 6 days after inoculation.

It was obvious, therefore, that a virus-inactivating substance or substances, freely diffusible through cellophane, were released when purified hyaluronic acid was hydrolyzed by hyaluronidase. No such substance was obtained on dialyzing unhydrolyzed hyaluronic acid. These observations have been confirmed using: (a) Levaditi virus (egg and testis passage) and dermo virus (egg- and cell-culture passage); (b) hyaluronic acid from several sources including vitreous humor; and (c) testicular and bacterial hyaluronidase. A reduction in titer was also observed when virus was treated similarly and titrated on the chick-embryo chlorioallantois, but in this case, particularly with fully egg-adapted strains, the effect was considerably less marked. Virus maintained in cell culture was inactivated by 2–3 passages in the presence of diffusate. Hemagglutinin titer of either egg-adapted or testis-passaged strains was reduced by 50–70% after 4 hr incubation with diffusate; again the fully egg-adapted strains were less affected.

Since the diffusible products released from hydrolyzed hyaluronic acid are N-acetyl glucosamine and glucuronic acid (either free or as oligosaccharides), we have examined the effect of the synthetic compounds on vaccinia virus.[5] In summary, all the described effects of diffusate could be duplicated by treating vaccinia virus with glucuronic acid under similar conditions (incubation at pH 6 for 4 hr at 37°, final concentration 2%). Again, virus inactivation was best shown in rabbit skin (Fig. 1); in chick-embryos the effect was barely significant. Cell-culture virus became inactive after 1–2 passages in medium containing 0.5% glucuronic acid. Free glucuronic acid and glucuronolactone at pH 5.5–5.9 were approximately equally as active in suppressing lesions in rabbit skin and in inactivating the hemagglutinin. Galacturonic acid showed approximately 50% of the activity of glucuronic acid, but sodium or potassium glucuronate, barium mannuronate, and N-acetyl glucosamine showed little or no activity in any test.

Although we have not yet rigidly excluded the possibility that a dialyzable impurity present in the various preparations of hyaluronic acid and glucuronic acid may be responsible for virus inactivation, the simplest explanation of the above observations would be to assume that vaccinia virus was specifically inactivated by glucuronic acid under the conditions described. That the action was directly concerned with the virus was seen from the observation that at least 4 hr incubation was necessary for complete suppression of infectivity: only partial suppression occurred after incubation for ½–3 hr.

Suppression of the virus in rabbit skin was, however, found to be reversible since the addition of hyaluronidase to an "inactive" mixture of virus and diffusate or glucuronic acid restored the treated virus to the same or a higher degree of activity than that shown by the control virus. This phenomenon explains the fact that, as shown in Table 1, the lesions induced after incubation of the virus with hydrolyzate and dialyzate were actually larger than the control lesions: the hyaluronidase still present in these materials, even after heating, reactivated the virus through spreading in the rabbit skin. A comparable phenomenon has been described when neutralized mixtures of vaccinia and antiserum were injected with hyaluronidase in the skin (*4*). The fact that the same virus-glucuronic acid mixture was significantly suppressed if titrated in rabbit skin, whereas a barely significant reduction in titer occurred in chick embryos, is in agreement with the interpretation that the effect in rabbits was due to reversible inactivation rather than destruction of the virus. Mixtures of vaccinia and antiserum inactive in the rabbit skin also became active when injected into the chick embryo or other tissues (*5, 6*).

It is possible that glucuronic acid interacts with vaccinia virus in a way similar to its conjugating action in detoxication mechanisms (*7*). If this is so, the

[5] We are indepted to E. R. Weidlein, Jr., and Corn Products Refining Company for gifts of pure synthetic glucuronic acid, glucuronolactone, and glucuronates.

acid or analogous compounds may play a part in defense mechanisms when the ground substance is attacked during infection. The experiments reported are being extended to other viruses and to bacteria.

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News and Notes

The Cooperative Research Foundation

Many programs have been developed in the past decade in the hope of increasing international understanding and cooperation in many different fields of common interest. Among these is an interesting experiment undertaken by a San Francisco group in 1950 which led to the establishment of the Cooperative Research Foundation, or CORE as it is commonly called. CORE is a true cooperative whose membership at present includes administrators, professors, scientists, and engineers from universities, research institutes, government agencies, and industry, both in the U. S. and abroad. The organization, with research offices in San Mateo and Washington, D. C., provides services through which scientists can exchange information, knowledge, and skills, through consultation and education, and can use available trained personnel and facilities to the greatest advantage in solving mutual scientific and technical problems. Members offer consultation, time, and facilities to other members, to government agencies, to universities, to research institutes and to industry.

During the past two years, CORE has been particularly active in building a cooperative program with the Conselho Nacional de Pesquisas of Brazil, an organization similar to the National Science Foundation in the United States. CORE's South American membership has grown rapidly through the leadership of such members as Admiral Alvaro Alberto, President of the Conselho, Dr. Cortes Pla, Head of the Science and Technology Section, Pan American Union, and Prof. Olympio da Fonseca, Director of the Instituto Oswaldo Cruz, in Rio de Janeiro. In the United States new members having interests similar to those of the Latin American members joined CORE to cooperate in the programs of the Foundation. To illustrate the type of direct working relationship developing between CORE members, a cooperative project in oil shale technology was initiated by one of CORE's board of directors, Prof. B. E. Lauer, Head of the Department of Chemical Engineering at the University of Colorado. For several years Prof. Lauer's department has been doing research on oil shale retorts which utilize fluidized solids techniques. Since Brazil is interested in making use of its extensive deposits of oil shale, CORE members in Brazilian universities became interested in the work at Boulder, and through travel grants awarded by the Conselho have spent short periods with Prof. Lauer in Colorado. Reports on the Colorado experiments have been sent to CORE members in several Brazilian research centers. The ground has thus been broken, through CORE's efforts, for a direct working level exchange of knowledge and mutual cooperation in oil shale technology.

Since its inception, CORE members have assisted the Conselho in placing the recipients of Brazilian fellowships and scholarships for graduate study in universities. In July of this year, with the cooperation of the California Academy of Sciences, CORE will open a San Francisco Liaison Office for the Conselho in the Academy buildings at Golden Gate Park. A committee of CORE members from the San Francisco Bay region has been formed to integrate the operation of this office with the scientific activities of the area. This committee includes Mr. Belford Brown, Vice President, The San Francisco Bank; Dean Morris Steward, Graduate School, University of California; Mr. George Tenney, President, McGraw-Hill Company of California; Dr. Robert Miller, Director of the California Academy of Sciences; Mr. R. L. Champion, U. S. Liaison Officer, Conselho Nacional de Pesquisas; Mr. John Alison, President, The Transit Van Corporation, and the writer. The committee plans to assist in obtaining fellowships for graduate study for Brazilian scientists who wish to attend universities in the area, to obtain subsistence grants and travel fellowships.

Later this year, with the cooperation of the National Academy of Sciences, the program of the office will be broadened to include a number of projects involving scientists from many different countries. By the end of the year a San Francisco International Relations Center for Scientists and Engineers will be in operation. The main functions of the center will be: (1) to facilitate contacts between the visiting scientists and appropriate scientific personnel in the area; (2) to serve as a liaison office between the National Research Council and the local scientific organizations and societies, and as a general coordinating agency for international scientific activities in the area; (3) to offer such other assistance to visiting scientists as other institutions of the area may not be equipped to give.

CORE serves as a structure through which members may participate in research projects requiring a rather highly specialized team of investigators. At the present time one team is in Korea studying a problem for the military and two other teams are engaged in operations research.

Because of their mutual interests in the availability of existing facilities, a team of fourteen CORE members last year assisted the National Academy of Sciences in a study of applied research in United States universities, research institutes, and foundations. The results were published as part of the National Academy of Sciences—National Research Council Publication 210, which was prepared for the use of the Mutual Security Agency.

As the Cooperative Research Foundation grows, its membership is becoming more broadly international. Although its largest membership is in the U. S. and Brazil, it now has members in England, Pakistan, Thailand, Peru, Mexico, and Argentina. Membership is open to all whose professional qualifications meet the standards set by CORE's membership committee. CORE's rapid expansion has been, in large part, due to the fact that it serves as a central agency through which its members from different countries can obtain help with special problems. This may be accomplished through consultation with colleagues who have specialized skills and knowledge of similar problems, through exchange of informative materials—books and films, through fellowships, scholarships, and study programs.

K. F. MEYER, *Director*
George Williams Hooper Foundation
University of California Medical Center

Scientists in the News

George B. Belloff has been appointed assistant to the medical director of Eaton Laboratories, Inc., N.Y., where he will supervise a research program in problems of veterinary medicine. He succeeds **Harold D. B. Roberts,** who is departing on military leave.

Reinhard H. Beutner, Visiting Professor of Physiology at the University of Arkansas School of Medicine and formerly Head of the Department of Pharmacology at Hahnemann Medical College, will join the staff of the Department of Physiology and Pharmacology of Still College of Osteopathy and Surgery, Des Moines, effective September 1.

Isaac A. Bigger, Professor of Surgery at the Medical College of Virginia, has been made President of the Southern Surgical Association.

Robert George Breckenridge, Chief of the Solid State Physics Section at the National Bureau of Standards, has been appointed Head of the Physics Branch of the Physical Sciences Division, Office of Naval Research, Washington, D.C.

Arthur Cherkin, Vice President and Director of Research, Don Baxter, Inc., Research and Production Laboratories, Glendale, Calif., has been awarded a Ph.D. in biochemistry by the University of California at Los Angeles.

Carey Croneis has been made Provost and Harry Carothers Wiess Professor of Geology at The Rice Institute, Houston, Tex. The appointment will become effective in Jan., 1954. From 1928 to 1944 Dr. Croneis was on the geology faculty of the University of Chicago, and since 1944 he has been President of Beloit College.

Gordon Dean, former Chairman of the U.S. Atomic Energy Commission, has become associated with the investment banking firm of Lehman Brothers, New York City. Mr. Dean has been an advocate of greater publicity of the destructive power of our atomic weapons. He has been a contributor to various legal and scientific publications and is the author of a forthcoming book entitled *Report on the Atom.*

Robert Reed Denison, former contact metallurgist with the Sheffield Steel Co., Houston, Tex., has been named a full research metallurgist at the Armour Research Foundation of the Illinois Institute of Technology.

Albert W. Dent, President of Dillard University, New Orleans, has been elected President of the National Health Council, New York City. He is the 14th president of the 32-year-old Council. He fills the unexpired term of **Robin C. Buerki,** whose resignation was accepted with regret. Dr. Dent has a long record of service in voluntary health and educational fields.

Donald W. Fisher, formerly Assistant Professor of Geology with Union College, Schenectady, N.Y., has been appointed Senior Paleontologist with the N.Y. State Museum and State Science Service at Albany.

Wallace E. Frank, formerly Senior Staff Engineer in the Chemistry and Physics Division of The Franklin Institute Laboratories for Research and Development, has been appointed Chief of the Bioengineering Section of that division. Mr. Frank will direct a group of engineers and physicists in applying the techniques of their professions to problems in such fields as surgical instruments, prosthetic devices, and, in general, to problems in medicine and biology.

Ford Kalil, Lafe F. Larsh, and **John F. McKown** have been added to the staff of the Los Alamos Scientific Laboratory of the University of California. Mr. Kalil, who has an Electrical Engineering degree and an M.S. in physics, is in the Laboratory's Health Division. Mr. Larsh and Mr. McKown are in the GMX Division.

Wilbur A. Lazier has been elected a Vice President and Technical Director of the Sprague Electric Co., North Adams, Mass. For nearly 20 years he was at the DuPont Experimental Station where he was in

charge of work on the high pressure synthesis of methanol and higher alcohols, the catalytic reduction of long-chain fatty acids, and the development of nylon intermediates. Later he became the first Director of the Southern Research Institute, Birmingham, Ala., and then Director of Chemical Research and Development for Chas. Pfizer & Co. of Brooklyn, N. Y. He has published numerous scientific papers and has been awarded over 100 U.S. patents on his inventions.

Benjamin H. Lyndon has been appointed Professor of Social Service and Educational Director of the new social work training program at New York University's Graduate School of Public Administration and Social Service. He has done research in public welfare administration and is a specialist in the field of child development and parent education.

Brig. Gen. Sam F. Seeley, MC, USA, Chief of Surgery at Walter Reed Army Medical Center, Washington, D.C., will leave this month for assignment to the Office of the Chief Surgeon, Headquarters of U.S. Army, Europe. General Seeley has been Chief of the Surgical Service at Walter Reed Army Hospital and Director of the Surgery Division in the Center's Army Medical Service Graduate School since July, 1949.

Captain C. W. Shilling, MC, USN, who has just completed a tour of duty in Washington, D.C., as Director of the Research Division of the Navy's Bureau of Medicine and Surgery and as Special Assistant for Bio Science in the Office of Naval Research, assumed new duties this month when he became the Senior Medical Officer at the U.S. Naval Academy, Annapolis. Dr. Shilling was recently awarded the Founder's Medal of the Association of Military Surgeons of the United States by former President Harry S. Truman for his outstanding contribution to military medicine.

Milton V. Veldee is serving as a consultant to the Stanford Research Institute of Palo Alto and to the Michael Reese Research Foundation of Chicago. Dr. Veldee, formerly a medical director in the U.S. Public Health Service and Chief of the Laboratory of Biologics Control, has resigned as Vice President and Medical Director of the Hyland Biological Laboratories of Los Angeles.

A. Wormall of England is making a three-month visit to Brazil where he is giving lectures and presenting a regular course at the University of São Paulo on the uses of radioactive isotopes in biological research. **E. S. Guzman-Barron** of the University of Chicago is also visiting the University of São Paulo and giving lectures and conferences.

At the Annual Meeting of the American Psychiatric Association **Gregory Zilboorg** received the Association's $1000 Isaac Ray award for his professional contributions to the field of legal problems connected with mental disorders.

Grants and Fellowships

A research team of University of Tennessee chemical engineers has received a $12,700 contract from the **Atomic Energy Commission** to continue its investigations on the effects of wetting on heat-transfer characteristics of liquid metals. The group, working under Robert M. Boarts, Head of the University's Chemical Engineering Department, is now entering its second year of work on the project. The newly authorized studies provide for investigations of effects of various liquid pressures upon heat-transfer characteristics and for studies of the chemical-metallurgical effects of mercury upon different metals.

Eli Lilly and Co. has recently awarded two grants, one to A. Sidney Harris, Professor of Physiology, Louisiana State University School of Medicine, and one to Ralph L. Shriner, Professor of Chemistry, State University of Iowa. Dr. Harris is directing a study of the action of cardiac drugs, and Dr. Shriner is conducting research on the synthesis of polymers from alpha-amino acids.

The Ford Foundation has made grants totalling $249,500 to 5 leading Americans universities to enable them to undertake self-surveys of their training and research programs for the scientific study of human behavior. A grant of $49,500 was made to Stanford University and $50,000 each to the University of Chicago, Harvard University, the University of Michigan, and the University of North Carolina. The grants are for the academic year 1953–1954.

Five new grants-in-aid have been approved by the **Muscular Dystrophy Associations of America, Inc.** They are: $4860 to Paul J. Vignos at Western Reserve University, Cleveland, for the study of "Muscle Enzymes in Progressive Muscular Dystrophy"; $8856 to John Taylor Ellis, Cornell University Medical School, New York, for the project "Studies on the Nature and Pathogenesis of Muscular Degeneration in Cortisone-treated Rabbits"; $8316 to T. S. Danowski, Children's Hospital of Pittsburgh, for the project "Muscular Dystrophy Survey Studies Preliminary to Trials of Purified Growth Hormones"; $3240 to Teru Hayashi, Columbia University, New York, for the project "Studies of Surface-spread Actomyesin Fibers"; and, $2330 to Robert E. Olsen, University of Pittsburgh, for the study of "Synthesis and Metabolism of Glycocyamine."

The University of Vermont College of Medicine has been awarded a grant of $13,867 by the **National Heart Institute** to expand the College teaching program in heart diseases. Third-year students will spend a period of time in each of two hospitals learning the various aspects of diagnosis and treatment in heart disease. E. L. Amidon, Professor of Medicine, will act as program director.

In the Laboratories

Fisher Scientific Co. has opened a New England office at 10 Brattle St., Cambridge, Mass.

The **General Electric Co.** has announced that in the next few years it plans to increase its scientific staff working on fundamental research by 50%, hence the present force of 1000 will reach 1500. Included in the expansion will be the addition of 180 scientists to the 270 now employed. The company has engaged in a post World War II program for expansion and modernization that will reach $1,100,000,000 by 1955. Already $120 million has been spent for improved facilities for research and advanced engineering development work.

The **Institute of Visual Research,** with Herman F. Brandt as Director, is now a division of the **C. H. Stoelting Co.,** Chicago. Dr. Brandt, a Fellow of the AAAS, is a former professor of psychology and is the inventor of various psychological instruments. The Institute serves as a clearing house for all information and instrumentation related to visual research and provides a consultation service especially for those carrying on research in the fields of ocular photographic and photo-electric recording.

Lab World, national news magazine of the clinical-scientific laboratory field, received two awards for editorial achievement in the fifth annual awards of achievement contest of the Western Society of Business Publications. The honors were: the Grand prize for publications under 48 pages for the "most outstanding editorial accomplishment"; and a special award for its Journal-Ease section as "the most outstanding regular department."

Meetings and Elections

The following societies are meeting under the sponsorship of the **American Institute of Biological Sciences** at Madison, Wis., September 6–10: American Bryological Society; American Fern Society; American Microscopical Society; American Phytopathological Society; American Society for Horticultural Science; American Society for Limnology and Oceanography; American Society of Parasitologists; American Society of Plant Physiologists; American Society of Plant Taxonomists; Biometric Society (ENAR); Botanical Society of America; Ecological Society of America; Mycological Society of America; National Association of Biology Teachers; Phycological Society of America; Potato Association of America; Society of Protozoologists; Society for Industrial Microbiology; Society for the Study of Evolution; Sigma Delta Epsilon.

Monday, Sept. 7.

General Meeting for all participating societies, sponsored by the Sigma Xi and the AIBS, commemorating the **Fiftieth Anniversary of the American Society for Horticultural Science.** Address by E. J. Kraus, Dept. of Horticulture, Oregon State College, Corvallis, Oregon. "Significance of Growth Regulating Substances in Agricultural Practice."

Tuesday, Sept. 8.

Joint Symposium, sponsored by the AIBS and the Society of Industrial Microbiologists.

BIOLOGY AND INDUSTRY

a. Francis J. Curtis, Vice President, Monsanto Chemical Company.
   The Impact of Chemistry on Modern Agriculture.
b. C. J. Nusbaum, North Carolina State College.
   Biological Aspects of the Tobacco Industry.
c. Asger F. Langlykke, Director of Research, The Squibb Institute for Medical Research.
   Industrial Applications of Microbiology.

Wednesday, Sept. 9.

Joint symposium of the American Phytopathological Society and the AIBS.

COOPERATIVE AGRICULTURAL RESEARCH IN THE WESTERN HEMISPHERE

I. Modern Maize in the Western Hemisphere.
   a. P. C. Mangelsdorf, Harvard University.
      Corn Races: Their Origin, Distribution and Implications.
   b. E. J. Wellhausen, Rockefeller Foundation, Mexico.
      Modern Corn Breeding and Production in Mexico.
   c. A. F. G. Brieger, University of São Paulo, Brazil.
      Development of Maize as a Modern Food Crop of South America.
   d. M. T. Jenkins, USDA, Beltsville, Md.
      Cooperative Uniform Testing of Corn Inbreds and Hybrids.
II. Wheat Rust Control, an International Problem.
   a. N. E. Borlaug, Rockefeller Foundation, Mexico.
      The Mexican Wheat Program Basic to North American Rust Control.
   b. W. F. Hanna, Canadian Dept. of Agriculture, Ottawa.
      Progress in the Control of Wheat Stem Rust in Canada.
   c. Jose Vallega, Institute de Fitotecnia, Argentina.
      Wheat Rust Races in South America.
   d. H. A. Rodenhiser and B. B. Bayles, USDA, Beltsville, Md.
      Cooperative Uniform Nurseries and Disease Testing.
III. Potato and Tomato Viruses and Late Blight in the Americas.
   a. John Niederhauser, Rockefeller Foundation, Mexico.
      Late Blight in Mexico and Its Implications.

b. L. E. Heiderick, Rockefeller Foundation, Bogota, Colombia.
Late Blight Resistance, Present Status.
c. Carlos Ochoa, Dept. of Agriculture, Peru.
South American Species and Races of Solanaceae and Disease Control.
d. S. P. Doolittle, USDA, Beltsville, Md.
Disease Control in the Tomato.
e. K. Silberschmidt, Dept. of Agriculture, São Paulo, Brazil.
Potato Viruses in the Americas.

IV. People, Pathogens and Progress in International Disease Control.
E. C. Stakman, University of Minnesota, St. Paul, Minn.

The following societies are planning field trips prior to the opening of the convention:

American Society of Limnology and Oceanography. Sept. 5 and 6.
Ecological Society of America. Sept. 5 and 6.
American Society of Plant Taxonomists. Sept. 5.
Mycological Society of America. Sept. 4 and 5.
American Bryological Society. Sept. 4, 5 and 6.

On June 16 the **American Society of Mammalogists** met in New York City and elected the following officers: president, William H. Burt; vice presidents, George H. H. Tate and Robert T. Orr; recording secretary, Randolph L. Peterson; corresponding secretary, Keith R. Kelson; treasurer, Caroline A. Heppenstall.

A three-day interdisciplinary conference under the sponsorship of the **Institute for the Unity of Science,** Boston, Mass., was held recently on the Berkeley campus of the University of California. Embracing the fields of psychology, philosophy, physics, and mathematics, the conference was organized by Egon Brunswik, Professor of Psychology at Berkeley; Herbert Feigl, Professor of Philosophy, University of Minnesota; Philipp Frank, Professor of Physics, Harvard University; and the late Hans Reichenbach, Professor of Philosophy at UCLA.

The Eleventh Annual **Pittsburgh Diffraction Conference** will be held at Mellon Institute, Pittsburgh, Pa., on November 5–6. Technical sessions are being arranged on instrumentation and methods, metals recrystallization and preferred orientation, and structure of polymers. Papers on general diffraction subjects will also be accepted. Contributed papers will be considered in the order in which they are received. Titles should be submitted to the Program Chairman, Mr. E. E. Wicker, U.S. Steel Corp., Research and Development Laboratory, 234 Atwood Street, Pittsburgh 13, Pa., *before Sept. 1.* Abstracts should be submitted by Sept. 21. For further information, and for a copy of the preliminary program when available, write to Dr. H. R. Letner, Mellon Institute, Pittsburgh 13, Pa.

Miscellaneous

The **American Dermatological Association** is again offering a series of prizes for the best essays submitted for original work, not previously published, relative to some fundamental aspect of dermatology or syphilology. Cash prizes will be awarded as follows: $500, $300, and $200 for first, second, and third place, respectively. Manuscripts, prepared as though for publication, must be submitted in triplicate *not later than December 1* to J. Lamar Callaway, Secretary, American Dermatological Association, Duke Hospital, Durham, N.C. Competition in this contest is open to scientists generally, not necessarily to physicians.

Nine countries have signed a Convention providing for the establishment of a **European Nuclear Research Center,** according to an announcement of the **United Nations Educational, Scientific and Cultural Organization.** These include Belgium, France, Britain, West Germany, Greece, Italy, the Netherlands, Sweden, and Yugoslavia. Denmark, Norway, and Switzerland have approved the plan and announced their intentions to sign the Convention soon. It will enter into force when seven States have ratified or adhered to it.

The basic program of the European Organization for Nuclear Research provides for the construction near Geneva, Switzerland, of an international laboratory designed for research on particles of high energy and on cosmic rays. The laboratory is to house what may be the most powerful atom-smashing cosmotron in the world, a huge accelerator that will be rated at thirty thousand million electron volts. There will also be a synchro-cyclotron with a rating of six hundred million electron volts. The plan is to pool the resources of European countries to create a research base for modern physics comparable to those in the U.S., something no Western European country could possibly finance alone.

The laboratory will take about seven years to build and equip, and the cost, to be borne by the participating countries, will amount to an annual total of approximately four million dollars. It is to be used exclusively for pure scientific research and not in the military use of atomic energy. All results will be published and made freely available. The Nuclear Physics Center will mark the first occasion that European States have set up a body responsible for organizing active scientific research in common.

Ceremonies held July 2 at the **Naval Research Laboratory** in Washington, D.C., commemorated thirty years of scientific endeavor. Since 1923 the laboratory has grown from four buildings and 100 employees to 50 major buildings and more than 3000 employees, plus a field test station on the shore of Chesapeake Bay. NRL is often referred to as "the birthplace of radar" and has made significant contributions to basic knowledge of metallurgy, atomic energy, the solar spectrum, the upper atmosphere, undersea warfare, firefighting, high- and low-temperature lubrication, and protective coatings for men and metal.

Technical Papers

Some Metabolic Responses of Dogs Having Low Body Temperature[1]

Steven M. Horvath, B. K. Hutt, G. B. Spurr, and G. E. Stevens

Department of Physiology, College of Medicine, State University of Iowa, Iowa City

The impression that valuable physiological information could be obtained from long-term studies conducted on homeothermic animals having a reduced body temperature has prompted a number of investigators to obtain such a preparation (*1–3*). Woodruff (*3*) concluded that dogs are unable to survive hypothermia sufficiently long to make protracted metabolic studies feasible. The longest period that he was able to maintain a dog with survival at a rectal temperature below 82° F (27.8° C) was 10½ hr. However, in one instance an animal was maintained at this level for 26 hr before succumbing. Similar experiments have been conducted in this laboratory during the past 2 years, and some success has been obtained in producing a preparation whose rectal temperature could be maintained at approximately 24 ± 1° C for periods up to 28 hr with survival.

The method employed, in brief, consisted of preliminary anesthetization of the dog with 30 mg/kg of Nembutal[2] to permit control of the initial shivering during cold exposure and the obtaining of control data for a 1-hr period in a control room having an ambient temperature of 26° C. The animal was then moved into another room where the temperature was approximately −10° C. The Nembutal generally inhibited the shivering usually observed, and the rectal temperature dropped rapidly to approximately 28° C, at which time the room temperature was raised to about 22° C, and by minor shifts of this environmental temperature, the dog's rectal temperature was stabilized around 24° C. Thereafter the animal remained very quiet, usually without exhibiting gross shivering movements until the room temperature was once again raised to initiate the rewarming processes. The animals recovered spontaneously and were fully awake and aware of events when their rectal temperature attained 28° C. One animal was studied in this manner on 5 occasions and apparently suffered no ill effects.

The neurological, chemical, cardiovascular, and other phenomena which were studied in these animals will be reported in detail in later publications. It is the intent of this report to call attention briefly to the metabolic activity and energy exchanges observed in two of the latest experiments. The heat production of these two animals was measured in one instance (animal B) by a direct oxygen consumption method, that of Benedict-Roth, and in the other (animal A) by analysis for CO_2 and O_2 in an aliquot of the expired air collected in a Tissot spirometer. Temperatures of the room air, walls, rectum, muscle, various skin areas, and blood were obtained at frequent intervals by means of suitable copper-constantan thermocouples and a recording Brown potentiometer.

Some of the pertinent data obtained in these two experiments are summarized in Table 1. Although the magnitude of the physiological alterations in these animals is readily evident, the remarkable constancy of the preparation can only be partially appreciated by the statement that the rectal temperature remained constant. Further evidence of this stability comes from the perusal of data obtained on heat production and heat loss. In animal B the heat production during a 35-hr period varied between 10.9 and 6.6 and averaged 9.2 Cal/M²/hr. Similarly, animal A had an average heat production of 11.3 Cal/M²/hr for the last 27 hr of the experiment. The reduction in heat production and the fall in rectal temperature observed in 18 experiments performed on 11 animals appeared to have an exponential relationship (Fig. 1). The line drawn

TABLE 1

OBSERVATIONS ON TWO ANIMALS WHOSE BODY TEMPERATURE WAS MAINTAINED AT A LEVEL APPROXIMATELY ONE-THIRD BELOW NORMAL

	Dog A (30 hr) open circuit		Dog B (38 hr) closed circuit	
Weight kg	19.0		24.3	
S.A. M²	0.80		0.99	
	Control	Low	Control	Low
Rectal temperature °C	36.7	23.6*	35.8	23.5†
Mean body temperature °C	35.8	22.7	34.5	22.5
Heart rate/min	84	36	114	44
Calculated heat content Cal/M²	705	448	690	451
Oxygen consumption ml/min	96	17	129	23
Heat production Cal/M²/hr	34.7	6.2	37.7	6.6
Respiratory rate, per minute	8	2	6	1
Respiratory minute volume L/min	2.0	0.2	2.5	0.5
Total heat loss Cal/M²	219		239	
Total heat production Cal/M²	436		416	
Theoretical total heat production Cal/M²	1048		1433	

* 28 hr at a rectal temperature within 1.5° C of this value. This animal was later used in other experiments.

† 37 hr at a rectal temperature within 1° C of this value. This animal died while being rewarmed.

[1] Aided in part by a grant from the Josiah Macy, Jr. Foundation.

[2] Owing to the lowered metabolic activity observed in these animals in the cold, the possibility that continued Nembutal activity rather than cold per se is maintaining these animals has been considered. Several other shorter-acting anesthetic agents have been employed, and the relationship of initial anesthesia and the cold stimulus will be considered in detail in a future publication.

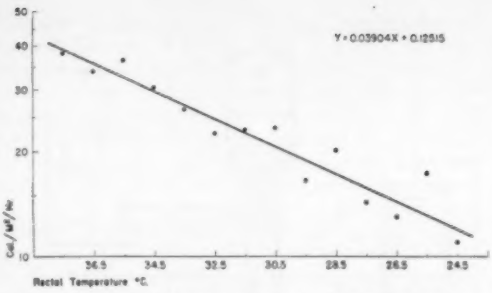

FIG. 1. Relationship between rectal temperature and heat production observed in 18 experiments on 11 animals.

through the observed data was fitted by the method of least squares. Application of van't Hoff's law to the warm-blooded organism within this temperature range would appear to be valid. Whether this observation can be extended to energy exchanges in separate organ systems cannot be answered at the moment, but studies are now in progress to elucidate this point.

Further and more comprehensive reports of the studies being conducted on animals maintained at this reduced and stable body temperature will appear shortly.

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Chemical Transformation of Steroids by Adrenal Perfusion VI. Allopregnane-21-ol-3,20-dione[1, 2]

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A multicycle perfusion of allopregnane-21-ol-3,17-dione (I) through isolated cow adrenals was performed a year and a half ago. In the course of working up the perfusate, difficulties in purifying the transformation products were encountered. Therefore a repetition of this perfusion was planned applying the newly developed processing techniques (*1*). Since, however, some time will elapse until this work can be started, and in view of a recent communication in which one of the transformation products of the above perfusion (allopregnanediolone) was described as a rat liver metabolite of desoxycorticosterone (*2*), it was felt that a preliminary report was advisable.

[1] This investigation was supported by a grant from G. D. Searle and Company, Chicago, Illinois.

[2] The acetoxyallopregnandione was donated by A. White, Chemical Specialties Company, Inc. Thanks are due to L. Ruzicka and H. Heusser for their generous cooperation. Infrared analyses and interpretations were kindly made by H. Rosenkrantz.

Purified I (m.p. 158–165°, $[\alpha]_D^{22} + 104.8 \pm 1.5°$ in chloroform) was readily converted by the surviving adrenals. Relatively little starting material was recovered. At least six transformation products at levels exceeding 1% were distinguished by their elutability in the silica gel chromatography. Of these, the following two have been identified.

The 11β-hydroxylated product, *allopregnane-11β, 21-diol-3,20-dione* (II), was found in relatively low concentration compared to the quantities of corticosterone formed in corresponding Δ^4-unsaturated desoxycorticosterone perfusions (*3*). Other 11-hydroxylated compounds might possibly be present, since several fractions were not identified. Hayano and Dorfman subsequently found with their beef adrenal residue preparation that I was converted to the 11β-hydroxylated derivative only approximately one half as readily as was desoxycorticosterone (*4*). The identification of compound II was completed as follows. An authentic sample of allopregnane-11β,21-diol-3,20-dione (*4*) was converted into the 21-monoacetate and found to be identical with the acetate of II (m.p. 189–192°) by mixed m.p. and infrared spectrometry. Absorption bands of a solution in carbon disulfide were found near 3460 (hydroxyl), 1751, and 1231 (acetate), 1730 (carbonyl at C.20), 1715 (carbonyl at C.3), 1087, 1054, and 1040 cm^{-1} (some fingerprint bands).

Another transformation product, obtained at a 15% level, was established as the reduced derivative *allopregnane-3α,21-diol-20-one* (III) as follows. After several crystallizations from ether, the m.p. 156–162° was attained. Admixed with compound I, a m.p. depression of 40° was observed; III showed the reducing properties of a steroid with a 20,21-ketol side chain toward silver ammonio reagent and was not precipitable with digitonin. Since the crystals appeared to be not entirely pure, the substance was converted to the acetate and yielded analytically pure leaflets with m.p. 165–166.5°, $[\alpha]_D^{27} + 98 \pm 2°$ (*c*, 0.710 in chloroform).

Analysis	$C_{25}H_{38}O_5$	Calcd.	C	71.75	H	9.15
		Found	C	71.66	H	9.21

These data suggested that this product was identical with allopregnane-3α,21-diol-20-one-diacetate (m.p. 165°, $[\alpha]_D + 92°$ in chloroform) (*5*). Ruzicka and Heusser kindly made a comparison of the acetate of compound III with their authentic material; the admixture did not produce an m.p. depression. Upon receipt of a sample of the authentic material, the identity of the substances could be substantiated by infrared spectrometry. Absorption bands of both samples in the solid state were found near 1739 and 1237 (ester groups), 1073, 1052, 1038, and 1019 cm^{-1} (some fingerprint bands). The keto group at C. 20 was only weakly resolved, visible by an inflection at 1710 cm^{-1}.

The formation of the corresponding 3β-hydroxyl derivative can for the moment not be excluded since several substances were not identified. In any case, its

presence would not exceed one-fifth the quantity of III on the basis of the weights of the two fractions with the presumable chromatographic polarity.

The formation of III, the 3α-hydroxyallo derivative, as a major transformation product of an adrenal perfusion is of particular interest, since reduced corticosteroids isolated from beef adrenal extracts have been found to have almost exclusively the 3β,allotetrahydro configuration. In fact, only the 3α,allotetrahydro derivative of 17α-hydroxycorticosterone has thus far been identified from this source (*6, 7*). Moreover, after adrenal perfusions of Δ^4-3-ketosteroids such as cortisone (*1*) only the 3β,allotetrahydro derivatives have so far been isolated. In these instances, the 3-ketoallodihydro derivatives were also found. The appearance respectively of the α- or β-epimeric saturated 3-hydroxy derivatives after adrenal perfusions of saturated and unsaturated 3-ketosteroids may suggest that these two structures undergo a sterically different course of biohydrogenation.

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A Remotely Controlled Pipetting Apparatus for Radioisotopes

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With increasing interest in the utilization of radioactive isotopes in biological experimentation and medical therapy, means for processing isotopes by remote control are essential to prevent exposure of operating personnel.

The two foremost health hazards that are involved in working with radioisotopes are danger from excessive radiation and the possibility of radiation from within the body as a result of ingesting radioisotopes. Under these conditions a remote control pipetting apparatus for handling "hot" solutions becomes a necessary item of equipment for most radioisotope laboratories. Although descriptions of some remote control pipetting devices have appeared in the literature and several are available commercially (*1–4*), the apparatus described here permits pipetting at a considerable distance from the operator without entailing a similarly long air column in series with the pipet, thereby minimizing the tendency for the meniscus to overshoot. Furthermore, this apparatus may be utilized not only with simple "distance shielding" but will also allow the operation to take place within a totally shielded enclosure for work at higher levels.

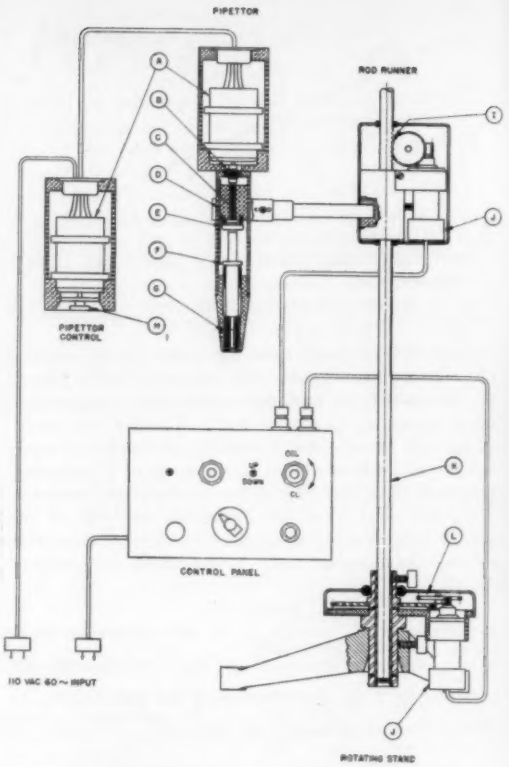

FIG. 1. A, synchro motors; B, flexible coupling; C, ¼—40 lead screw; D, keyed nut; E, self-aligning spring connection; F, hypodermic syringe; G, rubber grommet; H, control knob; I, rack drive; J, gear motors; K, framing rod; and L, gear reduction.

The pipetting device shown schematically in Fig. 1 makes use of three "building-block" appliances: a rotating ringstand, a rod runner, and the pipettor itself. These items are not available commercially but can be duplicated and combined to permit a variety of motions.

The rotating ringstand is a tube mounted in bearings on a tripod base, driven in rotation by a small dc gearmotor at speeds of from 0 to 3 rpm. The inside diameter of the tube was made ½ in. to permit the use of the common size laboratory rod. The control box contains a variable transformer and rectifiers to provide variable voltage dc power.

The rod runner (*5*), which is controlled from the same panel, contains a similar dc motor. A worm on the motor shaft engages a worm gear which is spring-loaded into a tapered groove in the rod to develop the necessary frictional driving force.

The pipettor is designed to accommodate glass hy-

podermic syringes in sizes ranging from 0.1–5.0 cc. For the insertion of various sizes of pipets, the rubber grommet of a Caulfield pipetting bulb is used. The plunger of the syringe is fastened to a long nut that is keyed against turning in the aluminum tube. A finely threaded lead screw engages the nut to impart the plunger motion. The lead screw, in turn, is rotated by a synchro motor that is housed in the large-diameter portion of the instrument and is electrically connected to a synchro generator (pipettor control) located next to the control box. Synchro instruments of the No. 3 frame size develop sufficient torque for this application.

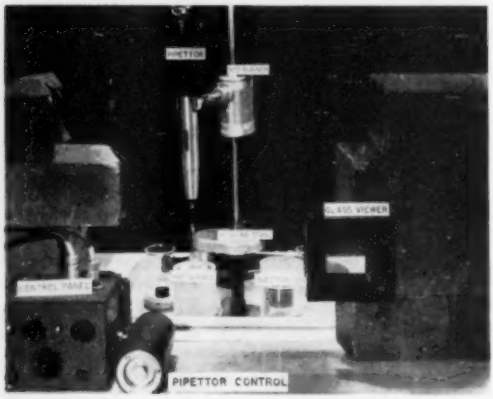

FIG. 2. A remotely controlled pipetting apparatus for the dispensing, diluting, and sampling of radioactive solutions.

These synchro instruments, which are sometimes available at low cost through electronic surplus houses, are not motors or generators in the usual sense. Connected by five wires of any reasonable length and excited with 110 v, ac, the motors of the two instruments follow each other's motions as if connected by flexible shafting. Turning the knob of the pipettor control in this application, thereby turns the lead screw of the pipettor an equal amount and can control the plunger position to within 0.0002 in. A small window is cut through the side of the tube, through which the gross motion of the plunger may be observed. When the plunger "bottoms" in the syringe the resistance to continued rotation is readily perceived at the control knob.

Figure 2 shows the pipettor,[2] rod runner, and rotating ringstand behind a lead shield in a typical laboratory experiment in which an experimental injection solution is being prepared from a "hot" source such as the stock isotopes received from Oak Ridge.

The 360° rotation of the rotating ringstand, the vertical motion of the rod runner, and the automatic pipettor provide all the necessary motions needed for the dispensing, diluting, and sampling of radioactive solutions. The accuracy of the delivered volumes with this apparatus compares favorably with that obtained by hand pipetting with the same pipets. Although the function of this apparatus has been described primarily for pipetting radioactive solutions, it can be advantageously applied where more complete manipulative facilities are not available, or where the required motions are sufficiently simple and repetitive to make its use desirable.

[2] The authors wish to thank Atlee S. Tracy for photographing this apparatus.

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The Effect of Progesterone on Rate of Phosphate Release from Adenosine Triphosphate by Rat Liver Homogenates[1]

Howard W. Jones, Jr., and Ruth Wade[2]

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Johns Hopkins University, Baltimore, Maryland

In a previous paper we have described the variation of phosphate release from adenosine triphosphate (ATP) by homogenates of human endometrium during the menstrual cycle (*1*). The ATP phosphate-releasing enzymes present in the endometrium show an increase of about 50% in activity from the fourteenth to the twenty-second day of the normal cycle, dropping off slightly in activity thereafter. Since the urinary pregnanediol curve has a peak at this same time, it was of interest to investigate further the influence of progesterone on the enzymes of the adenylic acid system. Rat liver homogenates were chosen as a source of the enzymes, as the alcohol used to dissolve the progesterone proved to inactivate partially the endometrial enzyme but had no detectable effect on the rate of ATP dephosphorylation by the liver homogenate. It is of course realized that the rat liver enzyme might be quite different from the human endometrial enzyme, but the results are nevertheless considered of sufficient intrinsic interest to record.

Methods. For the determination of the rate of phosphate release from ATP the method resembles that of DuBois and Potter for ATPase (*2*) except for the volumes employed. One-half molar barbituate buffer (*3*), 0.04 *M* calcium chloride, and distilled water were pipetted into a small beaker in the ratio of 3:1:2, respectively. When progesterone was to be added, it was first dissolved in absolute ethanol, and this solu-

[1] Aided by a grant from the American Cancer Society, Maryland Division, and the Katz Foundation.

[2] The authors acknowledge with thanks the courteous assistance of Dr. Leslie Hellerman.

tion was then substituted for part of the water so that the final concentration was 10% ethanol. Control studies showed the ethanol had no effect on the amount of phosphate released from ATP in rat liver. The pH was adjusted to 7.4, and 0.9 ml of this solution was pipetted into each tube with 0.45 ml of 0.015 *M* ATP (pH 7.4) and 0.6 of a 1% rat liver homogenate. Incubation time was 15 min at 37° C. The reaction was stopped by the addition of 0.3 ml of 50% trichloroacetic acid. The tubes were placed in the water for a few minutes and then centrifuged; 0.5 ml of the supernatant was used for inorganic phosphate determination by the Fiske and SubbaRow method (*4*). Tissue, reagent, and substrate blanks were made with all experiments, and the results subtracted from the experimental values.

The ATP used in the experiments was obtained from Schwartz laboratories in New York. It was stored in a desiccator in a refrigerator and separately weighed for each experiment. When the acid ATP preparations were fresh, increasing the concentration above 34.9×10^{-4} *M* had no effect on the rate at which phosphate was released. However, after storage for as little as 6 weeks, but mostly longer, the rate at which phosphate was released in 69×10^{-4} *M* ATP was sometimes irregularly greater. Also ethanol had no effect on newly ordered preparations but decreased the releasing rate of the older preparations considerably. We do not know the cause for this change. In this paper fresh acid ATP was used.

Rats from an inbred hooded strain from the Johns Hopkins Hospital were used in the experiments. No differences were found in the animals, although year-old female animals were usually chosen. Rats were killed by a blow on the head, and the tissue was frozen in isopentane cooled by liquid nitrogen. Tissues were stored at − 30° C until they were to be used. Experiments showed that no ATP phosphate-releasing activity was lost during such storage. At the initiation of each experiment a sample of the liver was weighed on a torsion balance, and a 1% homogenate made with distilled water.

Experiments. When progesterone was added to the incubation medium in the above manner, the rate of phosphate released from ATP by rat liver increased up to 65%, the increase depending upon experimental conditions (Fig. 1). The question immediately arises as to whether the increase is a direct effect, such as an enzyme activator, or the result of other reactions in which ATP participates in the metabolism of the hormone. In attempting the resolve this problem, several experiments were carried out as detailed below.

Variation of progesterone concentration. A series of experiments measuring the increase in the rate of phosphate release at various incubation times and progesterone concentrations was carried out. One of these experiments, representative of a group, is presented in Fig. 1. From these data it can be seen that the amount of "activation" with progesterone depends on the quantity of the hormone in solution. Ethanol

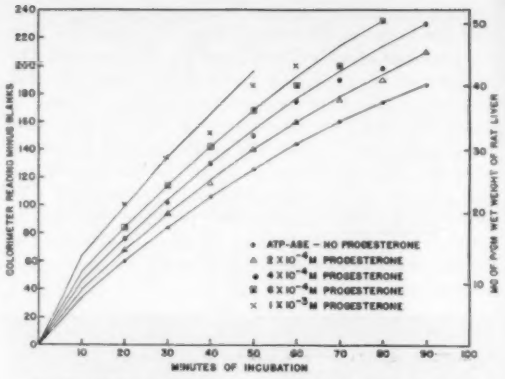
COLORIMETER READING MINUS BLANKS
MG OF P/GM WET WEIGHT OF RAT LIVER
MINUTES OF INCUBATION
ATP-ASE – NO PROGESTERONE
2 X 10⁻⁴M PROGESTERONE
4 X 10⁻⁴M PROGESTERONE
6 X 10⁻⁴M PROGESTERONE
1 X 10⁻³M PROGESTERONE

FIG. 1. Milligrams P/g liver in relation to time for various concentrations of progesterone. ATP 34.5×10^{-4} *M*; homogenate, 0.3%; pH, 7.4.

control samples corresponded with the experimental values for ATP phosphate-releasing activity without added progesterone. The solubility of progesterone in 10% ethanol is less than 2×10^{-4} *M*. In some experiments, crystals of progesterone could be seen forming in the tubes before addition of homogenate, and if allowed to come to equilibrium, no increase in the rate at which phosphate was released was found. The crystallization of progesterone at lower concentration does not occur after the homogenate is added. Therefore, the time required for adding the homogenate to each tube is critical. Because of this difficulty with progesterone solubility, higher concentrations than reported were not satisfactory. Therefore, the point of highest augmentation could not be experimentally determined. Because of solubility difficulties it is believed that the points of 1×10^{-3} *M* progesterone observed in Figs. 1 and 6 are irregular.

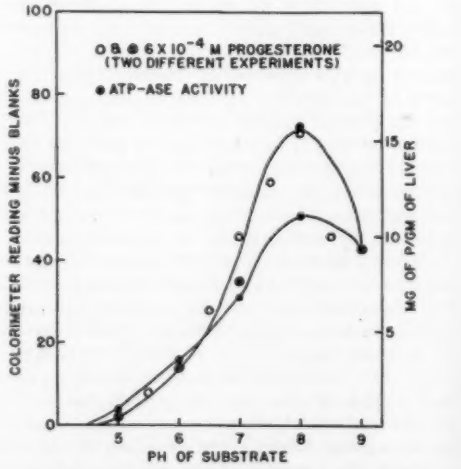

FIG. 2. Milligrams P/g liver in relation to pH with and without added progesterone. Time, 15 min; ATP 34.5×10^{-4} *M*; homogenate, 0.3%; progesterone 6×10^{-4} *M*.

Stability and inactivation. It is known that ATP phosphate release is stable in ice water for a number of hours, and heating the homogenate to 60° C for 15 min completely destroys the enzyme activity. The progesterone effect proved to be stable in ice water also, and when the enzyme activity was destroyed by heat, no progesterone effect could be noted.

Variation of pH. Data illustrating the findings of pH variation are presented in Fig. 2. The optimum pH for both ATP phosphate-releasing activity and the progesterone augmentation was pH 8. If reference is made to Fig. 1 for values of ATP phosphate-releasing activity between pH 7 and 8.5, it will be found that the rate increase by progesterone depends upon the ATP phosphate-releasing activity and is the same whether the ATP phosphate-releasing activity is limited by time or pH.

TABLE 1

EFFECT OF CALCIUM AND MAGNESIUM IONS ON PROGESTERONE AUGMENTATION OF PHOSPHATE RELEASE FROM ATP
(colorimeter readings)

Incubation medium	No added ions	Calcium		Magnesium	
		3×10^{-3}	6×10^{-3}	1.5×10^{-3}	3×10^{-3}
1. Barbiturate buffer 34.5×10^{-4} *M* ATP	56	27	21	62	46
2. Barbiturate buffer 10% ethanol 34.5×10^{-4} *M* ATP	58	34	25	62	50
3. Barbiturate buffer 10% ethanol 6×10^{-4} *M* progesterone 34.5×10^{-4} *M* ATP	81	57	31	82	58

Effect of calcium and magnesium ions. There has been much discussion in the literature concerning the effect of calcium and magnesium ions on ATPase (*5, 6*). Although calcium is a well-known activator of myosin ATPase, investigators have reported quite different results with the liver enzyme. DuBois and Potter (*2*) report an activation by both calcium and magnesium ions at 3×10^{-3} *M*. Our experiments indicate both to be inhibitory at this concentration. Swanson found the discrepant effect to depend on the ATP preparations used (*7*). All experiments reported here were done with the acid form of ATP from Schwartz laboratories in New York. Although this form is not of the highest purity, it was found to be satisfactory in this work, provided fresh samples were used. The detailed data of a single experiment with calcium, magnesium, and progesterone are noted in Table 1. These values are expressed as colorimeter readings, but the actual amount of phosphate released can be found by referring to Fig. 1. If the colorimeter readings in Table 1 for barbiturate buffer and ATP (row 1) are referred to the ATPase–no progesterone curve of Fig. 1, and the activity is found with reference to

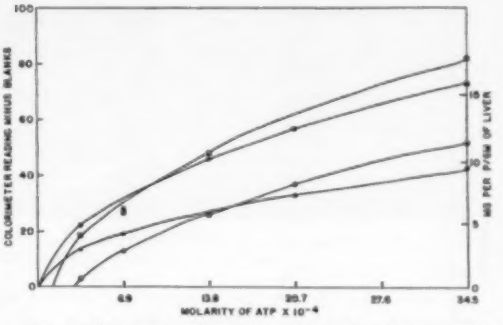

FIG. 3. Milligrams P/g liver in relation to molarity of ATP for 2 homogenate concentrations with and without added progesterone. Time, 15 min; pH, 7.4; ○ and □ progesterone 2×10^{-4} *M*; ● 0.3% homogenate; ■ 0.6% homogenate.

time, the progesterone augmentation of the rate is approximately the same for both experiments at 6×10^{-4} *M* progesterone (row 3, Table 1). Therefore, the data indicate that, regardless of whether the activity of the enzyme is controlled by calcium or magnesium, or pH, or time, the augmentation in rate depends upon the level of enzyme activity without progesterone.

ADP and AMP as substrates. In an effort to establish whether the influence of progesterone is specific for ATP, ADP, and AMP were substituted as substrates, using the same conditions. The 10% ethanol necessary for dissolving the progesterone reduced ADPase activity by more than 50% but had no effect on 5-nucleotidase. Progesterone had no detectable effect on the phosphate-releasing rate by either of the 2 enzymes.

ATP concentration. For further evidence as to the mechanism by which progesterone catalayzes the rate of phosphate released from ATP, experiments in which this substrate was a limiting factor were performed. At low ATP concentrations and 2×10^{-4} *M* progesterone, the hormone appeared to inhibit, rather

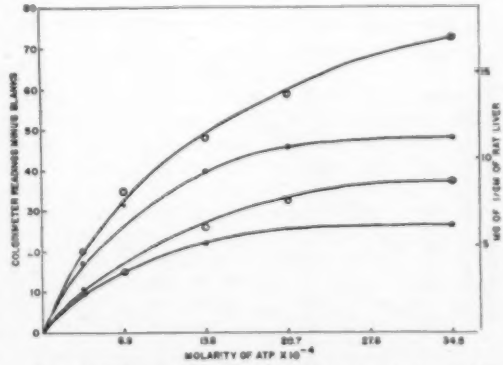

FIG. 4. Milligrams P/g liver in relation to molarity of ATP for 2 homogenate concentrations with and without added progesterone. Time, 15 min; pH, 7.4; ○ progesterone 6×10^{-4} *M*; ● 0.15% and 0.3% homogenate.

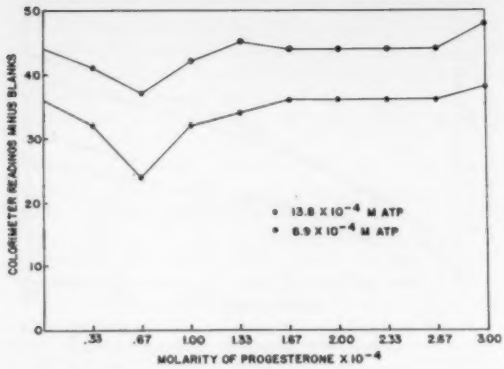

FIG. 5. Milligrams P/g liver in relation to molarity of progesterone for two ATP concentrations. Time, 15 min; pH, 7.4; homogenate, 0.03%.

than augment, the rate of the reaction. The point where no net effect was observed depended on the concentration of the homogenate. Data illustrating these findings are summarized in Fig. 3 at two different enzyme concentrations. However, when the progesterone concentration was increased to 6×10^{-4} *M* no inhibitory effect was found (Fig. 4). A third experiment in which a limiting amount of ATP was held constant and progesterone concentration was varied further supported the inhibiting effect of progesterone at low concentration. As the amount of progesterone was increased, the inhibiting effect was overcome, and an augmentation was noted at higher concentrations (Fig. 5).

Discussion. Under conditions of low substrate concentration, progesterone reduces rather than accelerates the amount of phosphate released. The amount of reduction is dependent not only upon the ATP concentration but also on the amount of enzyme present; thus 0.15% rat liver homogenate shows a much greater deceleration effect with progesterone than does 0.30% homogenate under the same conditions. If the same experiment is repeated at a higher progesterone concentration, 6×10^{-4} *M*, no reduction in the amount of phosphate released is observed (Fig. 4). The net progesterone effect is that of an activation of phosphate release (Fig. 6). It may, therefore, be concluded that the influence on phosphate release from ATP by progesterone is dependent upon the relative concentrations of ATP, progesterone, and enzyme in such a way that there must be more than a minimum concentration of any one of these 3 variables to cause a net acceleration.

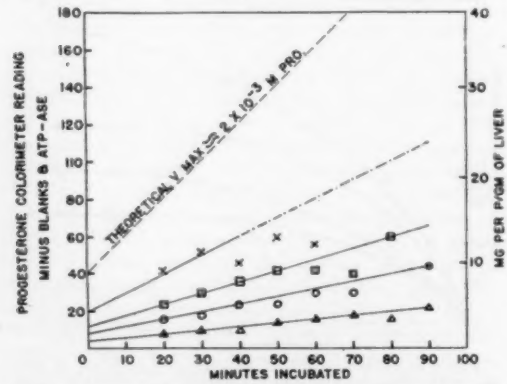

FIG. 6. Plot of net progesterone effect on phosphate release from ATP according to time.

These data lead us to believe that, although progesterone and ATPase of rat liver have a direct relationship, it is not simply that of an enzyme and its activator. This theory is further supported by the fact that, if in Fig. 1 the experimental ATP phosphate-release values are subtracted from those of progesterone, a series of straight lines results (Fig. 6). The Michaelis-Menten equation then becomes applicable.

$$\frac{V_{max}(S)}{V = K_s + (S)}$$

or

$$1/V = 1/V_{max}\ K_s/V_{max}\ 1/(S) \qquad (1)$$

V is the overall velocity of the enzymatic reaction; V_{max}, the maximum value of this velocity; (S), the substrate concentration (progesterone); and K_s the dissociation constant of the enzyme-substrate complex. It will be noted that Eq. (1) is a straight line in which $1/V_{max}$ is the y intercept and K_s/V_{max} is the slope of the line formed when $1/V$ is plotted against $1/S$. In this way the maximum velocity may be calculated. This velocity is found to be approximately 2×10^{-3} *M* progesterone.

The effect of progesterone may be represented by the following scheme:

$$\begin{array}{ccc} ADP + PO_4 + Pr(Pr') & & ADP + E + PO_4 \\ \quad \| \ (5) & & (2) \ \| \\ ATP \cdot Pr \cdot E & \underset{(4)}{\overset{Pr}{\rightleftharpoons}} & ATP + E \rightleftharpoons ATP \cdot E \\ \quad \| \ (6) & & (3) \ \| \quad (1) \\ AMP + E + 2PO_4 + Pr(Pr') & & AMP + E + 2PO_4 \end{array}$$

Our data indicate that the net velocity of the reactions by pathway (4) is more rapid than by (1), provided progesterone, ATP, and enzyme are present in sufficient concentration. However, with limited concentration of these 3 components, the combined net velocities of (4) and (5) or (4) and (6) are less than (1) and (2) or (1) and (3). This may be accounted for by assuming that there is a greater affinity for E for the ATP · Pr complex than for ATP alone, and that there is an appreciable accumulation of ATP · Pr · E.

It is to be noted that in this scheme alternate pathways: (2) and (5) on one hand, and (3) and (6) on the other, are suggested. Novikoff, Hecht, Podber, and Ryan (5) recently indicated that the enzyme in question is probably ATPase, but, in view of the possibility of an apyrase, the alternate pathway is shown.

It is further indicated that progesterone may be obtained from the reaction in an alternate state Pr′. Preliminary studies indicate that Pr′ is water soluble, but further studies are in progress on the nature of this change.

One of the most meaningful aspects of this study may be the *in vitro* demonstration of the effect of a hormone on an enzymatic reaction at a subcellular level. It is furthermore indicated that the participation of the hormone in the enzymatic reaction results in its alteration (metabolism!). This specific example may, therefore, illustrate a concept of wide application and significance.

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A Simplified Method for Cultivation of Poliomyelitis Virus in Tissue Culture

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Roller tube tissue culture methods, as described by Enders and associates (*1, 2*) and extended by others (*3–6*), have opened new vistas in poliomyelitis research by providing techniques more economical than previous methods, requiring the use of monkeys, for poliomyelitis virus isolation, virus typing, and the assay of specific antibodies.

However, there still remain a number of practical difficulties and limitations, and foremost among them are the ingredients of the medium. Tissues such as human embryo and monkey testes either are not always readily available or are expensive. Horse serum is frequently inhibitory to virus, and chick embryo extracts are at times sources of contamination. While search is continuing for a suitable substitute for monkey testes, currently the most commonly employed tissue, we wish to report briefly on some changes in technique. These modifications permit the rotary drum to be dispensed with, and, when monkey testis tissue is used, the chick embryo extract and horse serum to be replaced by plasma hydrolyzate with rather satisfactory results.

Shortly after tissue culture study with poliomyelitis virus was instituted at this laboratory one year ago, it was observed that rotation of the tissue cultures is not essential for adequate cell or virus multiplication. If the culture tubes are kept stationary in slanted position so that the fluid just covers the tissue embedded at the lower end of the test tube, the cells as well as the virus grow very well. Other workers have had similar experience (*7–9*).

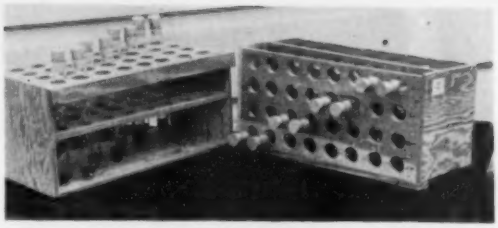


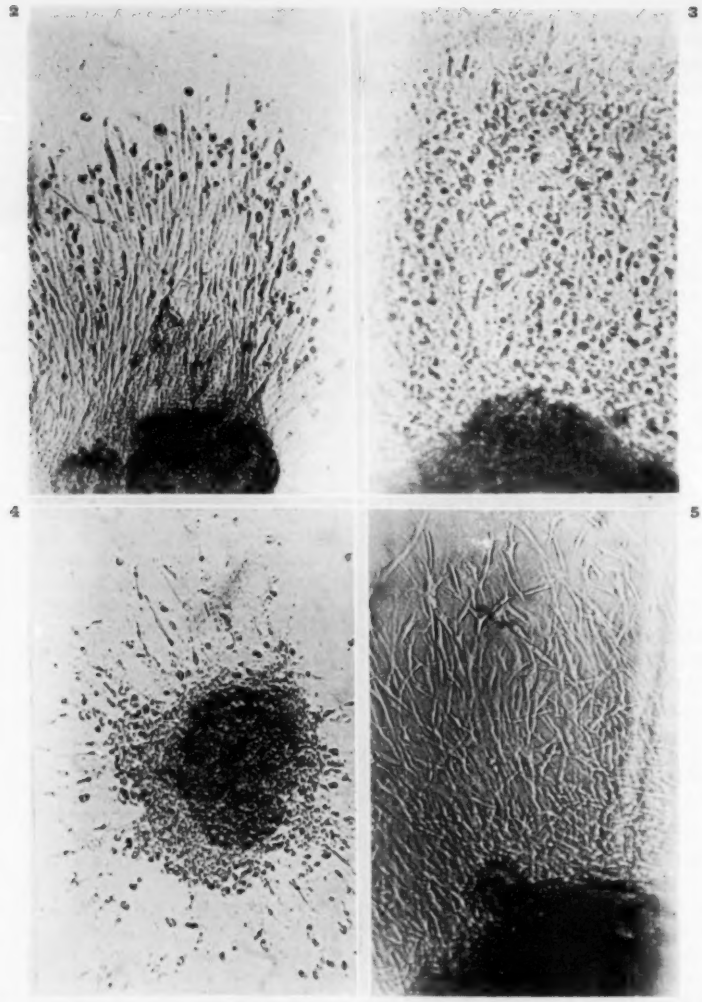
Fig. 1. Wooden racks holding tissue culture tubes in upright position or in slanted position.

Of a number of substances tested with a view toward replacement of chick embryo extract and horse serum, bovine plasma hydrolyzate[1] proved most satisfactory. Consequently, a medium incorporating this material was devised; it is designated Medium E. Medium E is rather simple, consisting of 75% Hank-Simms (Hank's 3 parts, Simms' 1 part) solution and 25% of the bovine plasma hydrolyzate. It is adjusted to pH 7.0–7.2 by the addition of sterile sodium bicarbonate solution. Recently it has been found that the Simms serum ultrafiltrate may be omitted entirely with equally good results.

The tissue cultures are prepared with fragments of monkey testicular tissue covered with 2 cc of the medium in ordinary bacteriological test tubes, 15 × 150 mm, similar to the techniques of Youngner, Ward, and Salk (*5*) and Ledinko, Riordan, and Melnick (*6*). The tubes are inserted into especially designed wooden racks, 11½ × 5½ × 5½ in., with holes for 4 rows of tubes, 8 tubes/row. When the rack is placed sidewise, a strip of wood about 1 cm thick across the upper back keeps the tubes in a slanted position at an angle of about 5° above horizontal level, and the medium just covers the tissue. When the tubes are moved from one place to another, the rack is carried in an upright position to prevent the fluid from touching the rubber stoppers (Fig. 1).

The cultures are incubated at 35° C for 5–7 days. No change of the medium is required during this period. The medium is then removed, and the virus, or other material desired to be cultured (in an amount of about 0.1 cc), is placed in contact with the cells for about 10 min, after which 2 cc of fresh medium is added. Incubation is continued and the cells are observed. With this procedure, both the fibroblasts and the virus grow well in Medium E, and, although the cells do not grow so richly and densely as those cultured in Medium A of Youngner, Ward, and Salk

[1] Obtained commercially as Travamin, a sterile 5% solution of bovine plasma hydrolyzate, w/v in water, from Baxter Laboratories, Inc., Morton Grove, Ill. Recently Melnick and Riordan (*8*) reported that lactalbumin enzymatic hydrolyzate is also satisfactory.



FIGS. 2–5. The cytopathogenic effect of poliomyelitis viruses on monkey testicular tissue culture Medium E without rotation, showing various degrees of cellular degeneration. 75 ×. Fig. 2. First degree of degeneration. Beginning degeneration of the periphery of the outgrowth zone. Twelve-day viral growth. (Mouse-adapted Type III Leon virus.) Fig. 3. Second degree of degeneration. Massive degeneration of the entire outgrowth. Four-day viral growth. (Tissue-culture-adapted Type I Mahoney virus.) Fig. 4. Third degree of degeneration. The outgrowth is almost entirely gone. The periphery of the mother tissue itself shows degeneration. Seven-day viral growth. (Tissue-culture-adapted Type I Mahoney virus.) Fig. 5. Control. Ten-day cellular culture without inoculation of virus.

(*5*), they are not granular as are those observed in Medium A. The pH of this medium does not drop so rapidly as does the medium containing chick embryo extract and horse serum. Consequently the number of necessary changes of medium is reduced.

The cellular degeneration caused by poliomyelitis viruses in Medium E is not only clearly defined but also, because nonspecific degeneration does not readily occur in uninfected tissue, the specific effects may be more easily recognized. There appears to be no difference in virus yield when this technique is compared to techniques employing the other media with and without the use of the rotary drums. For instance, a culture of Type I virus (Mahoney strain[2]) in Medium E without rotation yielded a pooled fluid with a tissue culture titer of 10^{-5}. This is the highest titer we have obtained as yet with any medium with or without rotation.

The cytopathogenic effects of the viruses on tissue culture cells in Medium E without rotation are shown in Figs. 2–5.

[2] Kindly supplied by J. E. Salk, Pittsburgh, Pa.

In a number of tests, cultures in Medium E without rotation have proved satisfactory for primary isolation of virus and for the performance of neutralization tests with the three types of poliomyelitis virus. Poliomyelitis viruses have been isolated from infected monkey cord, mouse cord, and human stools. One of the stool specimens was negative by monkey inoculation, but positive results were obtained by this tissue culture method. The fluid phase of this tissue culture, produced paralysis in two monkeys inoculated with it, and poliomyelitis was confirmed by histopathologic findings.

Neutralization tests, with the Mahoney strain as the test virus, have been performed by this method on a group of 80 human serum specimens with quite satisfactory results. In non-neutralized mixtures first evidence of cellular degeneration was usually observed on the second day after inoculation with the virus. This became fairly definite by the third day, and the final readings were possible on the fourth day.

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On a New Derivative of Thiamine with Cysteine

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The mechanism of thiamine in the metabolism in the living body is not yet clear. Zima and Williams (*1*) previously proposed a redox system between the thiol form of thiamine and thiamine disulfide.

The present authors have recently hypothesized a mechanism of thiamine in a medium that contains cystine, cysteine, glutation, or proteins having thiol groups, and have studied as a model experiment the reactions between thiamine and cystine, and between thiamine disulfide and cysteine by paper partition chromatography.

(1) Thiamine and equivalent cystine were dissolved in a phosphate buffer solution (pH 7.5), left standing at 37° C for 20 min, and then subjected to paper partition chromatography using the solvent prepared by shaking a mixture of alcohol, acetic acid, butanol, and water (1:1:4:10) and then drawing off the lower layer (Table 1).

The five paper strips on which the specimen was developed under the same conditions were dried in air and sprayed separately with the reagents indicated in Table 1.

The zones of Rf 0.04–0.05, 0.28–0.29, 0.29–0.31, and 0.36–0.38 correspond to cystine, cysteine, thiamine, and thiamine disulfide (VI), respectively. Besides these a new zone of Rf 0.14–0.15 was clearly detected by the reagents D, N, and I between the zones of cystine and thiamine.

When the paper strip sprayed with the reagent B was heated at 70–80° C for 5–10 min and then sprayed with the reagent A, the zone corresponding to thiamine showed strong fluorescence of thiochrome under the quartz mercury lamp, while the zones of Rf 0.14–0.15 and thiamine disulfide (VI) did not. However, when the paper strip was sprayed with the reagent C and heated at 70–80° C for 15–30 min in order to reduce the substances before spraying with the reagents B and A, all the three zones showed strong fluorescence.

From the result it seems evident that the new zone of Rf 0.14–0.15 means a new compound having the structure (IV) which was produced from the thiol form (II) of thiamine and cystine (III).

TABLE 1

Reagents	Cystine	Thiamine cysteine (IV)	Cysteine	Thiamine	Thiamine disulfide (VI)
D	—	0.14–0.15	—	0.29–0.31	0.36–0.38
N	0.04–0.05	0.14–0.15	(0.28–0.29)	—	—
I	0.04–0.05	0.15	—	0.30	0.37
B + A	—	(0.15)	—	0.30	—
C + B + A	—	0.14–0.15	—	0.29–0.31	0.36–0.38

D = the Kraut-Dragendorff reagent (*2*).

N = 0.2% solution of ninhydrin in the water saturated with butanol.

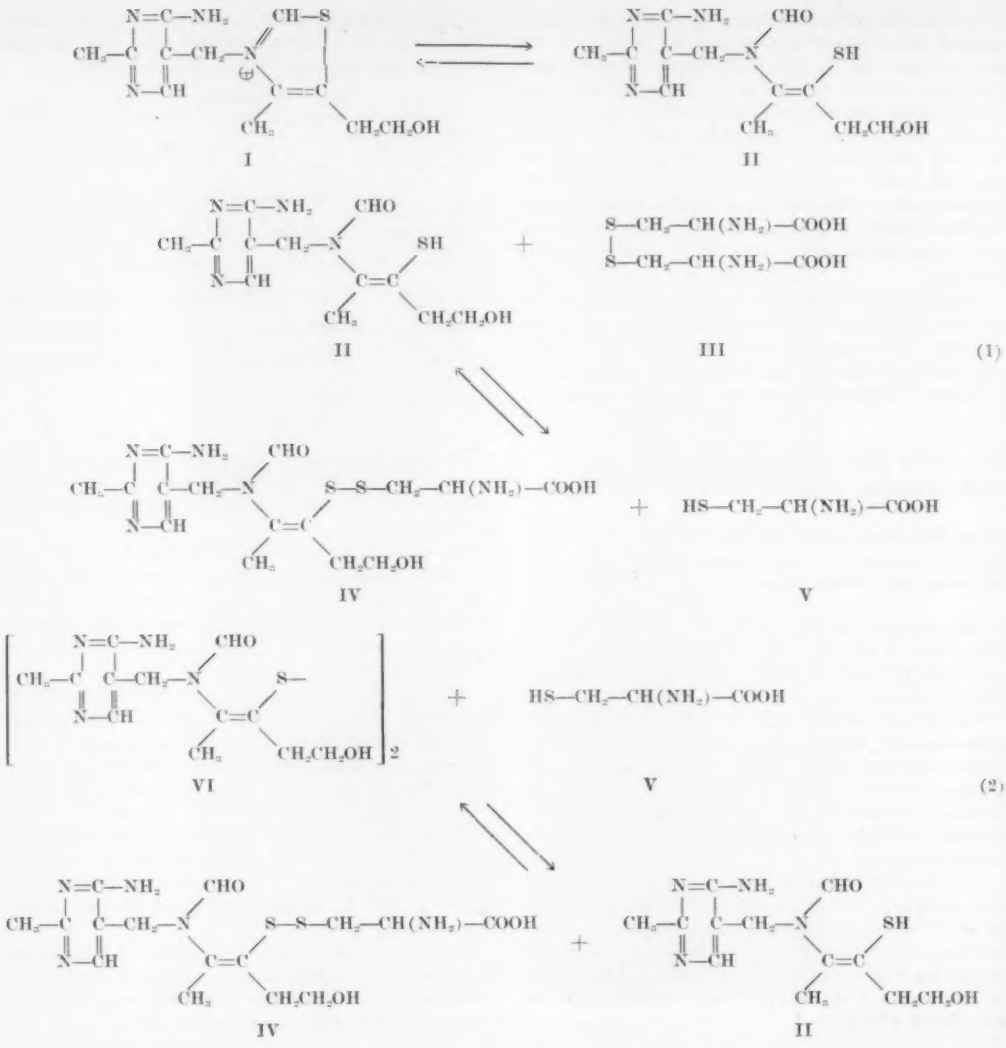
I = 0.05 *N* aqueous solution of iodine containing 1.5% of sodium azide. The reagent used for the detection of sulfur-containing amino acids (*3*) (thiamine and some related compounds can be detected by this reagent).

B = this reagent is prepared by adding 10% solution of sodium cyanide to the water saturated with bromine until the color of the bromine has disappeared (this is used instead of potassium ferricyanide to oxidize thiamine to thiochrome).

C = 0.4% solution of cysteine hydrochloride in water.

A = 5% solution of sodium hydroxide in the water saturated with butanol.

The mark (—) implies weak detection.



(2) Thiamine disulfide and equivalent cysteine were dissolved in a phosphate buffer solution (pH 7.5) and the solution was allowed to stand at 37° C for 20 min and then subjected to paper partition chromatography under the same conditions as in (1). The result was quite the same as that shown in Table 1.

From the above results the following mechanism might be suggested. Thiamine in a solution exists in a state of equilibrium between its ammonium (I) and thiol form (II) and the latter form takes part in the above reaction (1). In this reaction the thiol form (II) reacts with cystine (III) to produce thiamine cysteine (IV) liberating cysteine (V). The reaction will be an equilibrium one. In parallel with this reaction a secondary reaction (2) is imaginable in which (IV) reacts with the co-existing thiol form (II) to yield thiamine disulfide (VI) which in return reacts with cysteine (V) to form (IV), since the result of the reaction (2) is the same as that of the reaction (1). The secondary reaction will also be an equilibrium one.

These are, however, the results of the experiments carried out *in vitro* and with equimolecular substances. In the living body there is a large amount of cystine, cysteine, or their homologues, compared with that of thiamine; therefore, though the reaction (1) may be possible in the living body, the secondary reaction (2) seems impossible. In other words, the formation of thiamine disulfide (VI) seems unlikely in the living body.

From the results mentioned above it seems likely that the catalytic action played by thiamine in the metabolism in the living body is due to the following mechanism rather than to a redox system between the thiol form of thiamine and thiamine disulfide, proposed by Zima *et al.* Namely, an equilibrium reaction like (1) seems to be taking place in the living body, and the catalytic action of thiamine will be due to the dehydrogenating or oxidative action on certain substrata which are affected when thiamine cysteine (IV) or its homologues produced by the reaction revert to their original components.

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The Effect of Whole Blood Transfusion on Dogs Receiving a Maximal Sublethal (LD_0) Exposure to Ionizing Radiation[1]

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Allen and his associates (*1*) have reported the effects of whole blood transfusion in the treatment of the acute illness in dogs produced by whole-body x-irradiation. Their data show that 4 of 10 transfused animals died consequent to a 175-r exposure that was not lethal for the control animals. This suggests that in the lower dose levels of irradiation, transfusions may kill animals not fatally injured by irradiation.

A similar study is reported here to help define the hazard, if one exists, of compatible whole blood transfusion to the dog suffering acute radiation sickness following a maximal LD_0 total body exposure.

Twenty unanesthetized mongrel dogs were paired as closely as possible with respect to weight, sex, age, and blood type. Each animal was subjected to 300 r of whole-body x-irradiation from a 1-Mev machine. One of each pair, following irradiation, served as a control while the other received typed, crossmatched, compatible whole blood on a predetermined basis of three transfusions a week beginning on the 4th day postirradiation and continuing for 4 weeks. The blood was drawn from donor animals into standard ACD solution 48–72 hr prior to its administration, and stored at 4° C. Blood was transfused into a leg vein in an amount of 5 cc/kg of body weight at each transfusion. Sufficient blood was withdrawn from each animal 3 times weekly in order to determine its hematocrit, RBC, WBC, and platelet counts.

[1] This paper is based on work performed under contract with the United States Atomic Energy Commission and the Armed Forces Special Weapons Project at the University of Rochester Atomic Energy Project, Rochester, New York.

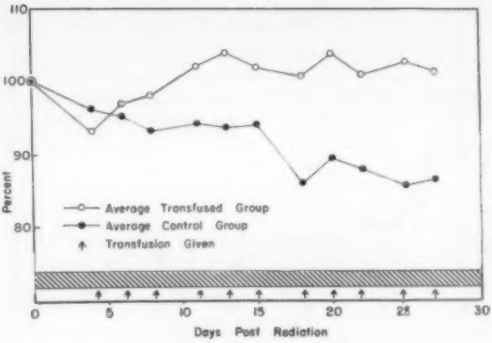

FIG. 1. Percentage preradiation hematocrit.

A fourteen-dog donor colony was maintained. Each donor and recipient animal was typed for the presence or absence of the canine A factor. A+ blood was given to A+ recipients and A− blood to A− recipients. The blood was crossmatched for major and minor incompatibility just prior to transfusion.

The diet of the donor colony was supplemented with daily feedings of horse meat and iron which maintained the donor hematocrits at approximately 95% of their control levels.

Results. Mortality: None of the animals in either group succumbed during the 28-day observation period.

Hematology: Figure 1 shows that the average hematocrit for the transfused dogs was restored to the preradiation value by the blood transfusions, whereas the control group's average hematocrit fell gradually in a linear fashion. The average platelet count (Fig. 2) and white blood cell count (Fig. 3) for the control and the treated groups were essentially the same.

Transfusion reactions: No clinical hemolytic or anaphylactoid reactions occurred.

Under the conditions of this experiment, the findings of Allen *et al.* could not be confirmed. Allen's x-ray factors differed from ours, but in both experiments the lethality of the exposure appeared to be

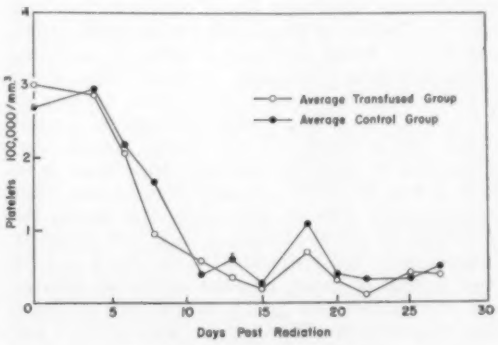

FIG. 2. Average platelet counts.

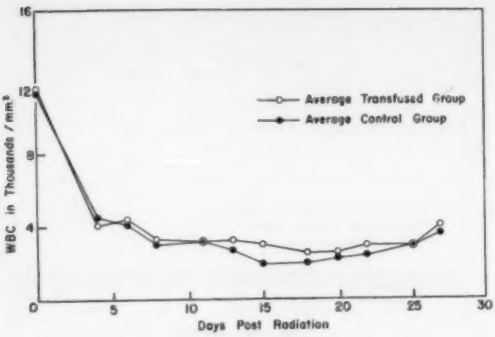

FIG. 3. Average leucocyte counts.

equivalent as determined by other dose-mortality data from each laboratory. In both instances the total body dose given appeared to be the greatest that could be administered in each laboratory without producing death (except in the rare highly susceptible dog).

Although the present experiment offers no direct evidence, it seems possible that the transfusion reactions encountered by Allen *et al.* may be responsible for the mortality of the otherwise nonfatally irradiated dogs. Incompatible transfusion, not fatal to the normal dog, may constitute an injury that is lethal to some of the irradiated animals. This point is under investigation in our laboratory at present.

Typing for the presence of the canine A factor in the erythrocytes of both donors and recipients and crossmatching were carried out on all transfusions of dog blood administered during the course of these experiments. We would take strong exception to the statement of Allen *et al.* that the blood groups of dogs are much less well defined than those of man. In the laboratories of the Department of Medicine of the University of Rochester up to the present time, 8 distinct dog blood-grouping factors have been demonstrated, and the respective isoantibodies characterized. The *in vivo* and *in vitro* characteristics of the first 5 of these have been described in detail in previous publications (*2–12*). These isoantibodies are produced by immunization of dogs with erythrocytes containing agglutinogens which they do not possess in their own red cells. The first of these antibodies described, canine anti-A, is a potent hemolysin capable of producing severe hemolytic transfusion reactions when either anti-A-containing plasma is given to an A+ dog, or A+ cells are given to a recipient immunized for this factor. The A factor is a very potent antigen, thus giving rise to potential hemolytic transfusion reactions in dogs subjected to repeated transfusions. Since approximately 65% of dogs carry this factor, the possibility of isosensitization is high with randomly chosen donors and recipients. Canine anti-A may be very difficult to detect in saline-containing systems, and crossmatches done by this method may not detect this incompatibility. Thus, proper choice of donor and recipient with regard to this factor is important if major hemolytic reactions are to be avoided in experiments involving transfusions of dogs with donor blood.

Anti-B, -C and -D behave as simple agglutinins and the corresponding factors are less antigenic than the A factor. Anti-E occupies a position intermediate between these two groups of antibodies in that under some circumstances it is capable of causing rapid destruction of donated cells. The detailed characteristics of these and the more recently encountered isoantibodies will be published elsewhere (*13*).

Using these precautions, we have administered over 400 therapeutic transfusions to irradiated dogs during the past year, many of which were given to previously transfused dogs, during the course of this and other experiments. We have seen no clinical hemolytic transfusion reactions in this experience, neither have we encountered anaphylactoid reactions with aggravation of the hemorrhagic diathesis of the irradiated dog. An occasional animal vomited or defecated following too rapid infusion of blood. However, we have been unable to detect evidences of hemolysis following such reactions. We do not feel that the irradiated dog is more susceptible than normal to transfusion reactions when compatible blood is administered. In experiments where therapeutic effects of transfusion are being measured it is very important that these precautions to minimize transfusion reactions be observed.

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Effect of Posture on the Elimination of Radon in the Breath[1]

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In persons retaining a substantial radium burden 1 year after contamination, over 95% of the radium is fixed in the skeletal tissues (*1*). A large portion of the radon which emanates from the radium is carried away by the blood stream as a dissolved gas. Much

[1] This work was supported by a grant from Atomic Energy of Canada, Ltd., Chalk River, Ontario.

of the dissolved radon diffuses into the air in the lungs and is exhaled. The rate of elimination of radon in expired air should be proportional to the radium content of the body. Therefore the amount of radon in exhaled air has been used to estimate the amount of radium present in the body, using empirical constants (*2*). The radon output in breath must, however, be subject to physiological variables. To study these variables we have used healthy subjects with a well stabilized burden of radium.

The subjects were males between 33 and 63 years of age, who were carrying appreciable amounts of radium but had not been working in any radium industry for more than 1 year. Special tests were devised to exclude the possibility of superficial contamination of the respiratory tract by particles of radium.

In preliminary experiments the subjects were seated comfortably in an armchair and were made to breathe through a BMR mouthpiece fitted with appropriate valves. A period of at least 10 min was allowed to flush the lungs with radon-free air.

Samples of approximately 6 l of expired air were collected in a gasometer at intervals of 10–12 min. Measurements were made of the volume of each sample and of the time required for its collection. From the gasometer the gas was transferred into 2-l Pyrex bottles by water displacement, and from there to the ionization chambers for alpha pulse counting (*3*).

After analyzing 125 samples from 4 subjects it became evident that in any 1 subject fluctuations in the elimination of radon, whether expressed as radon/l of breath or as radon eliminated/min, were significantly greater than the experimental error. In 3 of the subjects the maximum values exceeded the minimum values by a factor greater than 2. Sometimes great variations occurred in successive samples without any obvious change in the physiological conditions of the subject.

TABLE 1

RADON EXHALED IN SUPINE AND ERECT POSTURES

Subject		10^{-12} c/l of expired air			10^{-12} c/min of breathing		
		Supine 12th–45th min	Supine after 60 min	Erect	Supine 12th–45th min	Supine after 60 min	Erect
A	m	6.0	5.3	2.6	54.0	40.6	24.8
	S.D.	0.8	0.8	0.4	15.3	4.8	5.0
	n	6	9	5	6	9	5
B	m	3.8	3.8	1.9	22.8	20.8	12.7
	S.D.	0.3	0.3	0.2	1.6	2.7	1.0
	n	6	3	12	6	3	12
C	m	5.0	3.9	2.0	36.8	23.6	18.4
	S.D.	0.7*	0.3	0.2	10.3*	1.0	2.9
	n	2	6	4	2	6	4
D	m	0.54	0.53	0.25	5.3	3.7	2.3
	S.D.	0.09	0.02*	0.00*	0.1	0.0*	0.1*
	n	3	2	2	3	2	2
E	m	0.99	0.95	0.46	7.1	6.8	4.7
	S.D.	0.11*	0.00*	0.06*	1.3*	1.6*	0.7*
	n	2	2	2	2	2	2

m = mean, S.D. = standard deviation, S.D. with * = range, n = number of samples.

TABLE 2

RELATIVE RADON OUTPUTS*

Radon	Supine	Seated	Erect
Concentration in exhaled air	1	0.79	0.50
Exhaled/unit time	1	0.87	0.64

* Weighted averages, based on 90 measurements on 5 subjects. Supine figures refer to the 2nd and subsequent hours.

The effects of acid and alkaline diets, and of fasting and feeding, were studied and found to be neither large nor consistent. However, when the posture of the subjects was varied, large effects were observed consistently.

Experiments in the erect posture, i.e., with the subject standing or supported with the legs dependent, were conducted for as long as tolerated by the subject, which was usually about half an hour. Experiments in the supine posture were generally of 90-min duration but were extended in two cases to 3 and 6 hr.

In the supine posture both the radon content of expired air and the output of radon/unit time were consistently much greater than in the erect posture (Table 1).

In the supine posture the radon output and the range of fluctuation were greatest between the 12th and 45th min after lying down, but afterward the radon output dropped to a somewhat lower and fairly constant level with a smaller range of fluctuation. With the subject sitting in an armchair the radon output was lower (Table 2) and the fluctuations greater than in the stable phase of the supine posture.

Important physiological responses on assuming the erect posture include: (a) decreased cardiac output, (b) decreased circulating blood volume, (c) increased pulse rate, (d) pooling of blood in the legs, (e) increased interstitial fluid volume in the legs, (f) increased pulmonary ventilation, (g) increased volume of functional residual air in the lungs, and (h) peripheral vasoconstriction (*4–6*). The first 7 changes (a–g) should cause only transitory changes in radon output. We have, however, observed no tendency for the radon output to return towards the recumbent values either in the erect posture or in the much longer observations with the subjects seated. Thus our observations suggest that in the erect and seated positions a decrease occurs in the clearance of radon from the site of its production. We suggest that this is due to vasoconstriction in the bones.

To explain the irregular variations in radon output in prolonged experiments in the seated posture, we postulate irregular modification of the vasoconstriction in bones because of inevitable small changes in position assumed by the subject.

The greater radon output between the 12th and 45th min after lying down may be due to clearance

of dissolved radon from tissues where it has accumulated previously when conditions for clearance were less favorable. The practical implications of the present findings are that exhaled air for radon determination should be collected with the subject supine and the sampling should be done after he has been lying down for about 45 min.

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Ion Exchange Effect on Alkaline Phosphatase of Serum with Reference to Cancer[1]

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The utilization of ion exchange resins has been rather limited in clinical biochemistry (*1–4*). As far as we know, no detailed investigation of the effect of ion removal upon the alkaline phosphatase in human sera has been published. We report here the results of our studies on the effect of ion exchange upon the alkaline phosphatase of the serum of normal, of noncancerous, and of cancerous individuals.

The sodium form of analytical grade Amberlite IR-120 (H),[2] was prepared and dried in an oven at 37° C. The dry resin is suspended in distilled water immediately preceding use, and 1.5 ml of the resin is transferred to a 3-ml micro filter funnel with fritted disk of coarse porosity (Pyrex 36290). The excess water is aspirated by suction applied to the stem of the funnel. The serum is introduced into the funnel. The rate of flow should not exceed 1 ml/min, and not more than 8 ml is allowed to pass through the resin; the first 0.5 ml is discarded. The following determinations were made on the serum before and after passing it through the ion exchange resin: total protein (*5*), calcium (*6*), magnesium (*7*), sodium and potassium,[3] pH with the glass electrode using the Beckman model G pH meter, alkaline phosphatase using adenylic acid as the substrate (*8*), lipase (*9*), and diastase (*10*).

A comparison of the analyses of the resin treated serum and the untreated serum showed no changes in the total protein; more than 95% of the calcium and all the magnesium and potassium were removed. There was also a slight lowering of the pH of the serum. There were slight increases in the sodium. There were no demonstrable changes in the lipolytic or diastatic activity. There was a loss of alkaline phosphatase activity in the resin treated serum as a result of ion exchange.

The results of our experiments indicate that concomitant with the removal of divalent ions from the serum by a cation exchange resin there is a diminution of alkaline phosphatase activity, designated as Kase-Mg, both in the serum of noncancerous persons, and in those with a malignant tumor (Table 1). Since elevated serum alkaline phosphatase values are generally accepted as indicating either bone disease or liver damage, such cases were excluded from our series. The nonmalignant group was composed of 16 normal males and females, 5 cases of pregnancy, and 32 others known to be free from neoplastic disease.

The cancer group consisted of 46 individuals with some form of neoplastic malignant disease, in whom the diagnosis was confirmed by biopsy or post-mortem examination. The phosphatase was determined before surgical intervention or other treatment was instituted. These cases classified according to the site of the tumor are as follows: liver and pancreas 4, genitourinary system 18, gastrointestinal tract 20, breast 3, lung 3, and miscellaneous 3.

There is greater diminution of alkaline phosphatase activity of the serum of patients with neoplastic malignant disease, which cannot be entirely attributed to the fact that the initial alkaline phosphatase of the serum is usually increased in cancer, as shown in a previous communication (*8*); a comparison of the means of the Kase-Mg of the cancer and nonmalig-

TABLE 1

STATISTICAL ANALYSIS OF ALKALINE PHOSPHATASE ACTIVITY OF HUMAN SERUM AS A RESULT OF ION EXCHANGE

	No. of patients	All phosphatase values in mg%			
		Control phosphatase	Resin-treated phosphatase	Loss in phosphatase Kase-Mg	% change in Kase-Mg
Normal and nonmalignant	53				
Mean		2.3	1.45	0.85	37
Stand. Dev.		0.7	0.55	0.37	11
Range		1.0–4.5	0.5–3.1	0.1–2.2	7–52
Cancer	46				
Mean		5.0	2.9	2.1	44
Stand. Dev.		3.4	2.15	1.69	12
Range		1.9–18.7	0.8–10.8	0.6–5.8	28–80
Cancer with low alkaline phosphatase	13				
Mean		2.5	1.4	1.1	44
Stand. Dev.		0.3	0.27	0.31	11
Range		1.9–2.9	0.9–1.9	0.6–1.8	29–67

[1] Under a grant from the Lewis Memorial Fund.

[2] Rohm and Haas, Philadelphia.

[3] Flame photometer, Process Instruments Photometer, Brooklyn, N. Y.

nant group shows a statistically significant difference when the p value is calculated by the method of Fischer (*11*). This difference applies both to the absolute loss, and in terms of percentage of original phosphatase activity. In the 13 cases of cancer in which there was a low initial serum phosphatase (Table 1), a comparison of the Kase-Mg mean of this group with that of the noncancerous group also showed a statistically significant difference. Nine of the 13 patients with low initial phosphatase activity had malignancies of the gastrointestinal tract.

In 25 cases, no definite relationship between loss of phosphatase activity and changes in pH values was apparent under our experimental conditions. The addition of serum or resin treated serum to the buffered substrate employed resulted in no change in the pH of the substrate.

When serum was incubated with substrate for 24 hr, the dephosphorylation was 6-fold greater than that obtained in a 2-hr period, while that of the deionized serum was only twice as great as found in the 2-hr period. It is evident that the rate and amount of enzyme activity is definitely affected by the cation removal.

It is generally accepted that all phosphatases and phosphate-transferring enzymes require a metal for activation. However, as stated by Lehninger (*12*), an activating or inhibiting effect produced by a metal *in vitro* does not necessarily define a physiological function of the metal in question.

In order to determine the effect of adding the ions removed by the cation exchanger, K^+, Ca^{++}, and Mg^{++} were added, as the chloride, to the buffered substrate in the same concentration found in serum. Only the addition of Mg^{++} had any activating effect upon the phosphatase activity of the resin treated serum, causing a resurgence which approximated that of the original phosphatase under consideration. It appears that removal of Mg^{++} from serum has some inhibitory effect on the phosphatase activity. The Mg^{++} removed from the serum of both the normal and cancerous groups is of the same order of magnitude; therefore, it seems probable that alkaline phosphatase, as it exists in serum, consists of at least one magnesium activated fraction. This fraction designated as Kase-Mg is the one found to be statistically significant in the cancer group. Recently Gomori (*13*) has shown that alkaline phosphatases of the intestine consist of three fractions; two of these fractions were rapidly inactivated while acting on the substrate in the absence of Mg^{++}, whereas all three have different and specific rates of activation by Mg^{++}.

When serum is passed through a cation exchange resin there is a dimunition of alkaline phosphatase of both nonmalignant and cancerous individuals. The serum from patients with a malignant tumor seems to show greater loss of activity. The fraction involved is a magnesium activated one.

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Comments and Communications

Aphids Carried by Wind Currents

The footnote on page 714 of Science, **116** (1952), regarding the possibility of aphids being carried by wind currents from the west to Puerto Rico, apparently requires an answer.

This is not a matter of opinion, but rather of fact, and my original statement as to wind direction was based on close to 30 years' residence in Puerto Rico, most of the time at Río Piedras. The most conspicuous industrial landmark there is Central Vannina southwest of town. When it begins grinding sugar-cane in December or early January, the noise of its continuous operation, against the prevailing northeast trade winds, comes rather faintly to the town. But toward the end of the grinding season in late May and June, the wind direction may be reversed sometimes for several days at a time, and the noise of grinding becomes very noticeable. Householders are especially annoyed by the deposits of flaky, black soot of burned bagasse from its stack, which float down on washing hung out to dry. After the grinding season is over, in summer and early autumn, fierce rainstorms may be expected from the west and northwest, as one learns by experience after having to rescue furniture from a porch on the west side of the house.

The first outbreak of the green peach aphid on tobacco in Puerto Rico, observed by Mario Pérez at Cidra on January 3rd, 1951, was already sufficiently severe to have been noted by growers several weeks previously and quite possibly had required a considerable period of build-up to have reached conspicuous outbreak proportions. Of the weather that autumn, Glenn Stallard, Meteorologist in Charge, Airport Station, Santurce, Puerto Rico, in a letter to the writer dated January 22nd, 1953, states:

"Normally easterly winds extend up to 20,000 feet or higher over Puerto Rico during the summer, but the belt of east winds is occasionally reversed by the passage of a hurricane to the north of the island. Such was the case in 1950 when a hurricane passed northeast of the Virgin Islands on September 1–2 and was centered about 260 miles north of San Juan on September 3. The hurricane, an unusually severe one, produced westerly or southwesterly winds over Puerto Rico for about three days. For at least a part of the period, September 3–5, air flowing over Puerto Rico from the surface to 18,000 feet had previously passed over Hispaniola. It is possible that at some levels the air stream may have crossed eastern Cuba, but it is considered most unlikely that there was a previous recent history of the air over Florida."

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Received January 30, 1953.

Books for Israel

I SHOULD like to bring to the attention of my fellow scientists a project in which they can participate with the satisfaction that comes from the fostering of international growth of science and scientific communication. At the request of the United States Information Service, and under its sponsorship, a co-operative project, "Books for Israel," has been formed, as an expression of cultural good will between the people of the United States and the people of Israel. Its object is to supply textbooks in all branches of learning for the secondary schools, universities and institutes of this newest democracy.

American scientists need no reminder of the volume and quality of scientific work emanating from such laboratories as those of the Weizmann Institute, the Hebrew University, and the Technion, to name only the best known. The training of the newer classes of scientists is being severely handicapped by the inability of these Israeli institutions to acquire dollar exchange for the purchase of American textbooks.

The United States State Department is therefore sponsoring this project so as to help overcome this difficulty. Many individuals, institutional and industrial libraries, as well as book-publishers, have textbooks published since 1940 which have been superseded by newer editions, or represent duplications or overstock. These can well be used by the scientists of Israel. Gifts of these books will be appreciated far beyond any monetary value they may have to their owners.

We scientists can all join in this important contribution to international amity by sending such books to: Books for Israel, 115 King Street, New York 1, N. Y.

These may be sent via parcel post at book rates. Packages should be marked "Book Rate," which, from any point in the United States to New York, is $.08 for the first pound and $.04 for each additional pound. Since packages weighing up to seventy pounds are acceptable, it may be possible for some individual in any institution or organization to undertake the collection from his colleagues and thus save in shipping costs.

These books will be transmitted to Israel from funds supplied by the State Department's Point IV Project.

A list of technical and scientific subjects, in which texts are desired, is appended. Please note that these books should be in good condition and published since 1940.

Aeronautics, agriculture, applied chemistry, architecture, astronomy, aviation medicine, bacteriology, biochemistry, biology, botany, business management, chemical engineering, chemistry, civil engineering, dentistry, electrical engineering, engineering.

Firearms, first aid, food technology, forest products, forestry, geography, geology, gynecology and obstetrics, heat and power engineering, hospitals, human anatomy, industrial management, industrial medicine, mathematics, mechanical engineering, medicine, mental hygiene, metallurgy and metallography, meteorology, military and naval medicine, military science, mining engineering, miscellaneous technology.

Natural history, naval science, navigation, nursing, oceanography, personal hygiene, photography, physics, physiology, psychosomatic medicine, public health, safety engineering, sanitary engineering, shipbuilding, surgery, time and motion study, zoology.

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Received May 27, 1953.

A System of Nomenclature for the Varieties of Human Hemoglobin

RECENT studies have established the existence of three inherited variations of human hemoglobin (*1–4*). The occurrence of significant amounts of the fetal type of hemoglobin in a number of different anemias has also been demonstrated (*5*). Several different systems of nomenclature have been employed for the designation of the various hemoglobins thus far recognized.

On January 6, 1953, the Hematology Study Section of the Division of Research Grants of the National Institutes of Health sponsored a symposium on the general subject of hemoglobin abnormalities. One feature of that symposium was a consideration of the problem of nomenclature in this rapidly evolving field of investigation. There was general agreement on the need for a uniform and elastic system of designating the different kinds of hemoglobin. After considerable discussion of the various alternatives, it was agreed that the five varieties of hemoglobin thus far recognized be designated as follows:

1) Normal adult hemoglobin, or hemoglobin A, previously referred to as hemoglobin N (*5*), or hemoglobin *a* (*4, 6*). As subvarieties of normal adult hemo-

globin are recognized, they can be designated hemoglobin A_1, hemoglobin A_2, etc. (*6*).

2) Normal fetal hemoglobin, or hemoglobin F, previously also referred to as hemoglobin *f* (*6*, *7*). Again, with the discovery of normal subvarieties they can be designated hemoglobin F_1, hemoglobin F_2, etc. (*6*).

3) Sickle cell hemoglobin, or hemoglobin S, previously also referred to as hemoglobin *b* (*4*).

4) Hemoglobin C, previously referred to as hemoglobin *c* (*4*), hemoglobin III (*3*), or hemoglobin X (*8*).

5) Hemoglobin D, previously referred to as hemoglobin *d* (*4*).

It is suggested that as new varieties of hemoglobin are described, they be assigned letters of the alphabet in the order of their discovery, beginning with E, unless, as in the case of sickle cell hemoglobin, there is some outstanding associated hematological or clinical effect which will serve as the basis for a convenient mental association.

It is felt that adherence to this system, with the introduction of modifications only as necessitated by further discoveries, will tend to minimize confusion based solely on terminological differences.

The participants in the symposium:

AMOZ I. CHERNOFF
BEN FISHER
JOHN W. HARRIS
HARVEY A. ITANO
EUGENE KAPLAN
KARL SINGER
JAMES V. NEEL, *Chairman*

Hematology Study Section
Division of Research Grants
National Institutes of Health

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The First Law of Fluorescence

SLIGHTLY more than ten years ago, the present writer pointed out the "First Law of Fluorescence" (*1*). This was derived by reasoning analogous to the basic rule of photochemistry, known as the First Law of Photochemistry or the Grötthuss-Draper law. The latter law was first discovered in 1817 by Grötthuss; after an interval of about 26 years, this law was independently rediscovered by Draper; some 60 years later the Grötthuss-Draper law was quantified by van't Hoff.

In 1942 the First Law of Fluorescence was stated as follows: "*energy must be absorbed by a luminescent system before emission (i.e., luminescence) can occur*" (italics in original). An old reference has just come to my attention which establishes that this law is at most an independent rediscovery. In 1876 Eugene Lommel (*2*) published the following statement: "The general proposition can therefore be laid down, *that a body capable of exhibiting fluorescence fluoresces by virtue of those rays which it absorbs*" (italics in original).

Obviously, then, due credit for priority must be given Lommel, and any eponym must take this into consideration.

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Book Reviews

Methods and Principles of Systematic Zoology. Ernst Mayr, E. Gorton Linsley, and Robert L. Usinger. New York–London: McGraw-Hill, 1953. 328 pp. Illus. $6.00.

Zoological systematics, widely scorned a generation ago as a dusty routine, has recently come alive again. It is now being more widely taught, more earnestly discussed, and more intensely studied than ever before. One reason for renewed interest is that even the more limited aspects of the science are undergoing a revolution, from typological taxonomy to population systematics, a movement parallel to and strongly influenced by the shift from, strictly speaking, Mendelian genetics to population genetics. Another reason is that systematists have broadened their objectives. It has never been true, in spite of criticisms to that effect, that they were solely occupied in labeling specimens. It is, however, true that their wide concern with all phases of evolution, with comparative physiology, with ecological factors, and indeed with practically every aspect of biology is a relatively recent development.

In spite of all that renewed activity, there has been no general book on zoological systematics. Such a book is now provided by the skilled hands of an ornithologist at the American Museum (author of *Systematics and the Origin of Species*) and two entomologists at the University of California. Stress

is on methods. This is largely a "how to do it" book for the beginning systematist, with about half of the text devoted to procedure: collecting, identification, statistical methods, and working up the results for publication. The next longest section is devoted to nomenclature, "strictly a means to an end," as the authors note, but an essential means and one so legalistically complex that here the student particularly needs guidance. This excellent summary and commentary of rules and usages will, indeed, be useful also to the experienced taxonomist, especially as the subject is now again in a state of flux and there is no up-to-date edition of the International Rules.

The smallest part of the book (less than 60 pp.) is devoted to principles, strictly speaking. Even here the emphasis is more on laying a basis for practice than on exploring really fundamental theoretical concepts or following ramifications into broader aspects of the subject. Thus the book does not fully convey or pointedly contribute to the currently exciting broadening of the scope of systematics. It was, however, a valid decision to provide a sound foundation in methods and to leave more theoretical and more controversial topics for later and more individual expansion. That does not mean that the book is not abreast of the latest theoretical advances; many of them are briefly explicit and all are implicit here.

Joint authorship has ironed out individual idiosyncrasies and produced a well-rounded treatment authoritative in all its many aspects. There is some unevenness of style and level, with occasional bits downright childish and a few quite difficult, but on the whole the book is not condescending and yet should be comprehensible to any college student. Altogether, this is a fine job and one that was greatly needed.

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Fatigue and Fracture of Metals. William M. Murray, Ed. Cambridge, Mass.: Technology Press of the Massachusetts Institute of Technology; New York: Wiley, 1952. 313 pp. Illus. $6.00.

This book contains 14 papers that were presented at a special conference on fatigue and fracture of metals held at MIT in June 1950.

The subject matter covered by these papers is extremely broad, in keeping with the multitude of variables that determine the fatigue fracturing of metals. In addition, the subject of brittle fracture is considered beyond any immediate connection with fatigue. For example, brittle fractures in ships and temper brittleness are discussed and there is a paper on "Fundamentals of Brittle Behavior in Metals" by Dr. E. Orowan. However, the problem of fatigue is the focus of the book, and the subjects treated include: fatigue in aircraft, ships, and machinery; designing for fatigue, with separate considerations of internal stresses and cumulative damage; statistical aspects of fatigue; transition temperature and fatigue; fatigue at high temperatures, and techniques of physical metallurgy for studying fatigue damage. The paper on the effect of metallographic structure by Major P. L. Teed is written in an especially refreshing style.

This book makes a worth-while contribution to the problem of fatigue by summarizing much of the contemporary knowledge and by indicating pertinent questions for future research. Since the book will undoubtedly find extensive use as a monograph on fatigue, it is unfortunate that an index was not prepared. Also, the readers of the book are denied the stimulation of the discussions of the individual papers and of the general panel discussions that were important parts of the conference.

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Purdue University

The Theory of Homogeneous Turbulence. G. K. Batchelor. New York: Cambridge Univ. Press, 1953. 197 pp. Illus. $5.00.

Homogeneous turbulence refers to a fluctuating random fluid motion whose average properties are independent of position in the fluid. The basic problem is to understand the mechanics and to determine analytically the average properties of this kind of motion. Dr. Batchelor has presented a systematic review of established knowledge of homogeneous turbulence. He has treated the problem from the point of view of the applied mathematician or theoretical physicist. With the qualification that he has leaned heavily on the research carried out at Cambridge, he has tried to make his account as complete as possible.

Chapters include a mathematical representation of the field of turbulence, the kinematics of homogeneous turbulence, some linear problems, the general dynamics of decay, the universal equilibrium theory, the decay of energy-containing eddies, and probability distribution. A good bibliography is given. Some experimental data are presented for comparison with the theoretical studies.

This book is limited to incompressible flow. The kinds of turbulent motion which are found in nature are usually more complicated than homogeneous turbulence. There are various complicated effects, as the effects of boundaries, that are extremely difficult to handle mathematically. We have not yet obtained a clear understanding of these complicated effects. The author treats a simplified case which makes the analysis simpler.

This book should be very useful to anyone wishing a good review of previous work in the field of homogeneous turbulence.

R. C. Binder
Department of Mechanical Engineering
Purdue University

Association Affairs

Hotel Headquarters, Seventh Boston Meeting, December 26–31, 1953

Raymond L. Taylor

Associate Administrative Secretary

THE preliminary announcement of the Seventh Boston Meeting of the AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE (SCIENCE, **117**, 613 [1953]; THE SCIENTIFIC MONTHLY, **76**, 315 [1953]), which was principally concerned with the programs of this year's 120th Meeting, named the headquarters hotels of the AAAS and the zoological societies (Statler), of the geneticists (Sheraton Plaza), and of the science teaching societies (Bradford). The detailed list of the headquarters hotels of all participating societies and of each AAAS section was scheduled to appear at this time when data on hotel rates could also be announced.

As in recent years, the center of the Association's annual meeting is a large convention hall—this year, the Mechanics Building—which houses the Main Registration-Information Center, the Visible Directory of Registrants, the Annual Exposition of Science and Industry, the AAAS Office, and the AAAS Science Theatre. In this building will be held the two general symposia of the Association, nearly all of the programs of the 18 sections of the Association—e.g., physics, chemistry, geology and geography, botany, psychology, the social sciences, engineering, and medical sciences (including medicine, dentistry, and pharmacy)—the illustrated lecture of the National Geographic Society, important conferences on scientific editorial problems and scientific manpower, and the Biologists' Smoker.

As usual, the sessions of the participating societies, principally, will be in four hotels chosen for their adequacy and relative convenience to the Mechanics Building, which is at 111 Huntington Avenue, two blocks west of Copley Square. The basic pattern of the session arrangements for the participating societies is the logical one of grouping specialists and closely related organizations in the same hotel to ensure maximum convenience for those attending concurrent sessions and similar programs. With respect to housing, the additional hotels named are close to those designated as headquarters. All hotels are listed by *zones*: hotels of the Copley Square area are close to Mechanics Building; of the hotels which are downtown, the Statler is three blocks east of Copley Square, the Bradford and Touraine two blocks further; in a northwest direction, the Somerset and Kenmore in Back Bay are a shorter distance from Mechanics Building. By underground trolleys along Boylston Street, no one is more than 5 to 10 minutes from meeting rooms in Mechanics Building or from the extremes of these hotels.

The hotels of Boston have agreed to provide ample housing at moderate rates. Housing will be handled by the well-directed and efficient Boston Convention Bureau. Hotel room assignment-confirmation slips are typed in quadruplicate, and one of these will be sent directly to the applicant. Those who apply early are assured the hotel of their first choice, but it must be remembered that the supply of single rooms at minimum rates is always relatively limited—it pays to apply early for them. Higher priced singles and double rooms for single occupancy are more plentiful. It is desirable that *maximum rate* be stated, as well as desired rate, on application forms. Expenses can always be reduced if rooms or suites are shared with one or more colleagues or friends. Special attention is called to dormitory accommodations—3 to 5 comfortable rollaway beds in a large room with private bath—at $2.75 to $3.00 per person per night.

Beginning with this issue, the advertising section of SCIENCE will carry page announcements of the hotels and their current rate schedules, together with a coupon which should be filled out and sent, ***not to a hotel,*** but to the AAAS Housing Bureau in Boston. Applications for hotel reservations will be filled in the order of their receipt.

Individuals of course have freedom of choice of hotels, but, in stating their preference, the desired rate, and the maximum rate, it is natural that those who apply latest may not secure their first choice of hotels. Usually a person's preference is for the hotel that has been named as headquarters for his section or society, but the hotels in the same zone are nearby. For the convenience of those planning to attend the 120th Meeting of the Association, the headquarters for the 18 sections and subsections and the participating societies are listed here:

HOTEL HEADQUARTERS

Downtown Zone

Statler: (1,300 rooms) Park Square	AAAS; Press; AAAS Sections C, F, I, Nm, Nd, Np; Alpha Chi Sigma; American Society of Zoologists, Herpetologists League, Massachusetts Zoological Society, Society for the Study of Evolution, Society of Systematic Zoology; Alpha Epsilon Delta, American Association of Hospital Consultants, American Institute of Nutrition, American Physiological Society; American Association of Colleges of Pharmacy, American College of Apothecaries, American Drug Manufacturers Association, American Pharmaceutical Manufacturers Association, American Pharmaceutical Association, American

	Society of Hospital Pharmacists; American Book Publishers Council, American Textbook Publishers Institute, Conference on Scientific Editorial Problems, National Association of Science Writers, Scientific Research Society of America, Society of the Sigma Xi, United Chapters of Phi Beta Kappa.
Bradford: (400 rooms) 275 Tremont St.	Academy Conference; AAAS Cooperative Committee on the Teaching of Science and Mathematics; AAAS Section Q; National Speleological Society; American Nature Study Society, National Association of Biology Teachers, National Science Teachers Association.
Touraine: (200 rooms) 62 Boylston St.	
Parker House: (700 rooms) 60 School St.	
	Copley Square Zone
Sheraton Plaza: (500 rooms) Copley Square	AAAS Sections G, H, L, O; American Eugenics Society, American Society of Human Genetics, American Society of Naturalists, Beta Beta Beta, Ecological Society of America, Genetics Society of America; American Society of Plant Physiologists, New England Section; History of Science Society, Institute for the Unity of Science, Philosophy of Science Association.
Copley Square: (124 rooms) 47 Huntington Ave.	
Lenox: (175 rooms) 61 Exeter St.	
Vendome: (300 rooms) 160 Commonwealth Ave.	
	Back Bay Zone
Somerset: (500 rooms) 400 Commonwealth Ave.	AAAS Sections A, B, D, E, K, M, P; American Meteorological Society; Association of American Geographers, Geological Society of America, National Geographic Society; National Academy of Economics and Political Science, Pi Gamma Mu; American Industrial Hygiene Association, Society for Industrial Microbiology; American Geophysical Union, Conference on Scientific Manpower, Committee for Social Physics, Society of Exploration Geophysicists.
Kenmore: (400 rooms) 490 Commonwealth Ave.	

Advance Registration and Advance Copies of the General Program-Directory

As in past years, those who plan to attend the meeting may register in advance and receive both a Convention Badge and a copy of the General Program-Directory, by first-class mail, early in December. The registration fee of $2.50 includes postage. Those who cannot attend the meeting but would like an advance copy of the General Program-Directory may also obtain it by first-class mail early in December at cost—$1.50. A coupon covering both alternatives will be found on another page in the advertising portion of this issue of Science. The appropriate square should be checked.

Sectional Sessions for Contributed Papers

Another section of the Association—Section L—has requested the publication of a call for contributed papers. The following is a complete list of the 10 AAAS sections which will receive short papers on current research. In general, a brief abstract should accompany each title and these should be sent each section secretary or program chairman, ***not later than September 30***—preferably earlier.

C, Chemistry—Dr. Ed. F. Degering, George Washington Inn, New Jersey and C Streets, S. E., Washington, D. C.

E, Geology and Geography—Dr. Jack B. Graham, 3400 North Westmoreland Street, Falls Church, Va.

G, Botanical Sciences—Dr. Stanley A. Cain, School of Natural Resources, University of Michigan, Ann Arbor, Mich.

H, Anthropology—Dr. Gabriel Lasker, Wayne University, 1512 St. Antoine Street, Detroit 26, Mich.

I, Psychology—Dr. William D. Neff, Department of Psychology, University of Chicago, Chicago 37, Ill.

L, History and Philosophy of Science—Dr. Raymond J. Seeger, 4507 Wetherill Rd., Washington 16, D. C.

Nd, Dentistry—Dr. Russell W. Bunting, School of Dentistry, University of Michigan, Ann Arbor, Mich.

Np, Pharmacy—Dr. George F. Archambault, Pharmacy Branch, Division of Hospitals, Federal Security Agency, Public Health Service, Washington 25, D. C.

O, Agriculture—Dr. C. E. Millar, Department of Soil Science, Michigan State College, East Lansing, Mich.

Q, Education—Dr. D. A. Worcester, University of Nebraska, Lincoln, Neb.

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Beyond these two that are familiar to millions of amateurs there is *Kodak Ektachrome Film*. It comes in roll and sheet film form, and you (or a local lab) convert it to a transparency. If you'd rather have a print to look *at*, we can make you a *Kodachrome Enlargement*, provided your original is 4″ x 5″ or less. If it's larger, we suggest a print by the *Kodak Dye Transfer Process*. This you can undertake yourself or leave to a commercial laboratory for a creation of smashing visual impact.

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Your Kodak dealer sells all these items and also the Kodak Color Handbook ($4) *that delves deeply into the details. Write Eastman Kodak Company, Rochester 4, N. Y., if you have any difficulty finding out what you want to know.*

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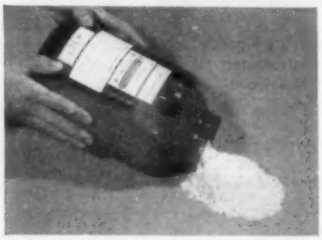
We've just made up a new batch of *3-Methylcholanthrene*, and here it is, in its entirety. The synthesis we use was first published by a man full of honors in polycyclic chemistry. It starts with chlorotoluene. Condense with chloropropionyl chloride. Close the ring to give the chloromethylhydrindone. Reduce to the corresponding chloromethylhydrindene. Replace the chloro group with a nitrile group. Add an α-naphthyl group to the nitrile group. Pyrolyze to *3-Methylcholanthrene*, which is Eastman 4383 in the catalog of Eastman Organic Chemicals and

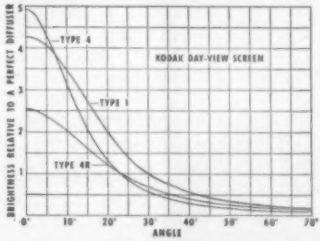


happens to be one of six carcinogenic hydrocarbons we produce for qualified cancer investigators who don't like to badger their synthetic organic chemical colleagues to go through operations like this for them.

There are more than 3500 other Eastman Organic Chemicals in the catalog. If the copy in your lab isn't marked "List No. 38," you had best drop a note to Distillation Products Industries, Eastman Organic Chemicals Department, Rochester 3, N. Y. (*Division of Eastman Kodak Company*).

Rear projection

Any intelligent schoolboy knows that to look at a projected real image up close without getting in the way of the beam you catch the image on a diffuser like a ground glass. As the schoolboy grows into an optical engineer, he learns that a) the better the diffusion the more light is likely to be wasted into space where there are no eyes to profit from it and b) ground glass really doesn't diffuse very well, being prone to a "hot" center and



dark corners for the image. As the engineer pursues the subject, he gets involved in the theory of field lenses, the light economy of high overall transmission, the contrast-enhancing value of light-absorbing material to counteract ambient illumination, the question of graininess, and the matter of over what angle the image is to be seen. Eventually he hears about Kodak Day-View Screens, a light-scattering dispersion in gelatin on glass.

Type I is white, of high transmission, with twice as much light transmitted at 30° as ground glass transmits. Type IV is rather black, which improves contrast substantially at high (but not at low) ambient levels. Type IVR is green, which is supposed to be more restful to the eyes in constant use. The curves, below left, give brightness *vs.* angle on a scale where unity represents the reflectance of a perfect diffuser.

Looking at the curves may be of some help, but it's no substitute for actually trying the three types of screens in any application you may have in mind. If seriously interested, write Eastman Kodak Company, Special Products Sales Division, Rochester 4, N. Y.

Flashed densities

Generally we sell our film unexposed, but even to that there is an exception. We refer to *Kodak Flashed Densities*, used for cutting down light by a specific fraction. They're plain sheets of precisely exposed, precisely processed, and precisely calibrated film (not to be confused with *Kodak Wratten Neutral Density Filters*, in which diffuse density nearly equals specular density).

One application is in equipment for patrolling the smoke output of distant chimneys by comparison with adjacent sky seen through the film. To a wider audience than just smokestack inspectors, we announce that we can supply any flashed density from .05 (89% transmission) to 4.05 (0.009% transmission), with a density tolerance of ± 3% or ± .02 in density, whichever is greater. Maximum usable area is 7½″ x 9½″, including holes at the corners. Prices vary from $2.75 for 4″ x 5″ size in the .05 to 1.05 density range, up to $25.25 for 8″ x 10″ in the 3.06 to 4.05 density range.

If any questions about Kodak Flashed Densities *occur to you, drop a note to Eastman Kodak Company, Industrial Photographic Sales Division, Rochester 4, N. Y.*

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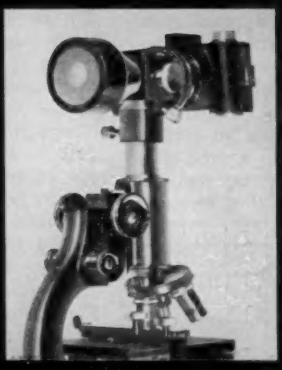

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Meetings & Conferences

July 27–Aug. 1. International Congress of Psychology. Paris.

July 27–Aug. 1. International Association of Psychotechnology, 11th Congress. Paris, France.

July 29–30. International Symposium on the Chemistry of Natural Products. Wayne University, Detroit, Mich.

July 29–Aug. 4. International Congress of Pure and Applied Chemistry and International Union of Pure and Applied Chemistry. Stockholm.

July 29–Aug. 4. Joint Commission on Physico-Chemical Data and Standards, International Council of Scientific Unions. Stockholm, Sweden.

July 29–Aug. 5. International Conference on Parapsychological Studies. Utrecht, Holland.

July 30–Aug. 1. Wyoming Geological Association. University of Wyoming, Field Conference. Laramie.

Aug. 1–7. International Astronomical Congress. Zurich, Switzerland.

Aug. 3. International Union of the History of Science, Third General Assembly, and International Congress of the History of Science, Seventh. Jerusalem.

Aug. 3–5. Abnormal and Pathological Plant Growth. Brookhaven National Laboratory, Upton, L. I., N. Y.

Aug. 3–8. 4th International Astronautical Congress. Zurich, Switzerland.

Aug. 3–8. World Meteorological Organization, Regional Assoc. for North and Central America, First Session. Toronto, Canada.

Aug. 4–8. Photographic Society of America. Los Angeles, Calif.

Aug. 4–12. 7th International Congress for the History of Science and 3rd General Assembly of International Union for the History of Science.

Aug. 5. Symposium on Macromolecules. Uppsala, Sweden.

Aug. 5–12. International Congress of Zoology. Copenhagen.

Aug. 7–8. Pennsylvania Academy of Science (Summer). Thiel College, Greenville, Pa.

Aug. 9. International Veterinary Congress (15th). Stockholm.

Aug. 10–14. Society of American Bacteriologists (Annual). San Francisco.

Aug. 10–18. American Association of Colleges of Pharmacy (Annual). Salt Lake City, Utah.

Aug. 11–13. International Atomic Power Congress. Kjeller, Norway.

Aug. 11–14. Canadian Teachers Federation, Alpine Inn, Ste. Marguerite, Quebec, Canada.

Aug. 12–18. International Congress on Home Economics (8th). Edinburgh, Scotland.

Aug. 15–30. Summer Seminar Workshop in General Semantics (10th). Institute of General Semantics, Lakeville, Conn.

Aug. 16–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Radcliffe College, Cambridge, Mass.

Aug. 16–22. American Pharmaceutical Association. Salt Lake City.

Aug. 16–22. American College of Apothecaries. Hotel Utah, Salt Lake City, Utah.

Aug. 16–22. American Society of Hospital Pharmacists. Salt Lake City, Utah.

Aug. 16–26. International Conference on Soil Mechanics and Foundation Engineering (3rd). Zurich and Lausanne, Switzerland.

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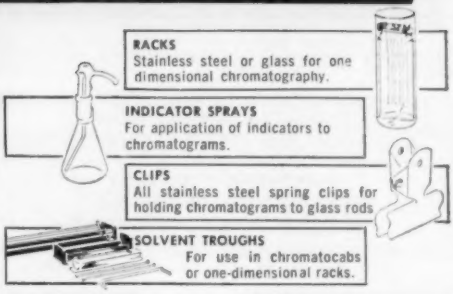

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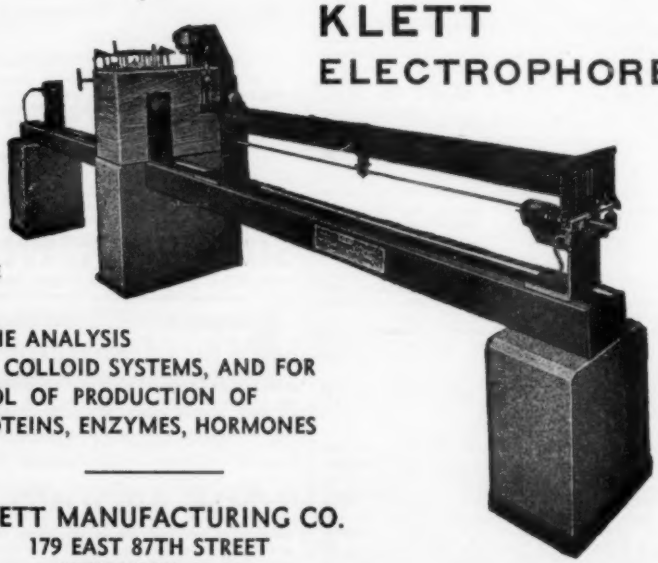

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Biochemist: Associate professor, 11 years' teaching experience in medical biochemistry and immunology. Approximately 30 publications in enzymology, immunochemistry, protein chemistry, nutrition, clinical chemistry. Desires teaching and research appointment in medical school, or research appointment in hospital or other medical research institution. Box 140, SCIENCE. 7/31; 8/7

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Physician, M.S. in biochemistry, experienced in research. Age 35. Box 139, SCIENCE. X

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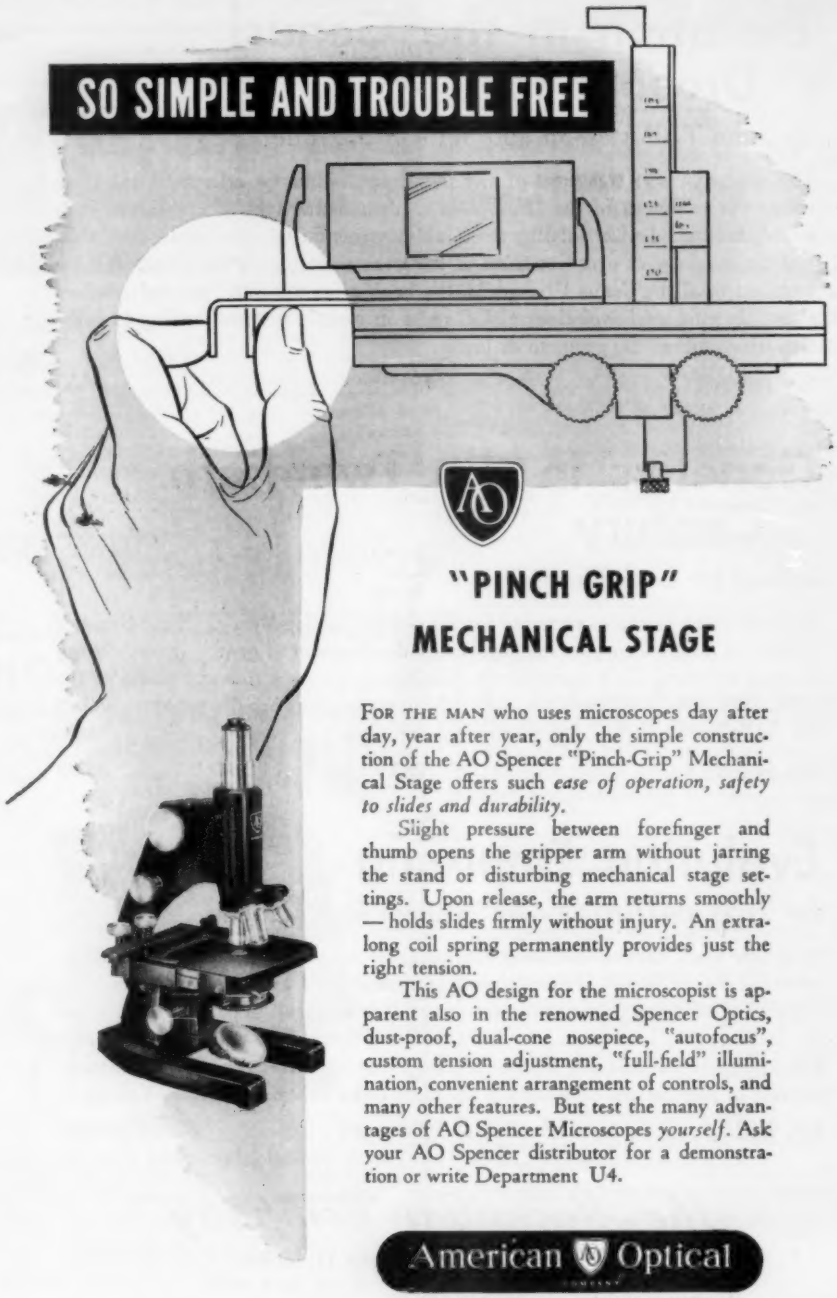

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